Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/JP05/003081

International filing date: 18 February 2005 (18.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/555,809
Filing date: 24 March 2004 (24.03.2004)

Date of receipt at the International Bureau: 14 April 2005 (14.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

PCT/JP2005/003081

25. 3. 2005

PA 1284714

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 16, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *60/555,809*
FILING DATE: *March 24, 2004*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. Lawrence

T. LAWRENCE
Certifying Officer

Express Mail Label No.: EV328703078US
Date of Deposit: March 24, 2004

Attorney Docket No. 25371-030 PRO

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR § 1.53(c)

INVENTORS/APPLICANTS

Given Name (last name, first name, and middle initial [if any])			Residence (City and State or Foreign Country)
Nakamura	Yusuke		Kanagawa, Japan
Nakagawa	Hidewaki		Tokyo, Japan

TITLE OF THE INVENTION

COMPOSITIONS AND METHODS FOR TREATING PANCREATIC CANCER

CORRESPONDENCE ADDRESS

Attorney Name: Firm Name and Address:	Ingrid A. Beattie, Ph.D., J.D. MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C. One Financial Center Boston, MA 02111
Telephone:	(617) 542-6000
Fax:	(617) 542-2241

ENCLOSED APPLICATION PARTS

☒	**Specification**	Number of Pages: 32 pages
☒	**Sequence Listing**	Number of Pages: 44 pages
☒	**Drawings** (☐ Formal; ☒ Informal)	Number of Sheets: 8 pages; (Figures 1-8)
☐	**Other** (Please Specify)	Number of Pages:

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government:

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

METHOD OF PAYMENT

☒ A check in the amount of **$160.00** is enclosed to cover the filing fees of the Provisional application.

☐ The Commissioner is hereby authorized to charge **$160.00** is enclosed to cover the filing fees of the Provisional application to Deposit Account No. 50-0311, Reference No_____.

☒ The Commissioner is hereby authorized to charge additional fees or credit any overpayment to Deposit Account No. 50-0311, Reference No. 25371-030 PRO.

Respectfully submitted,

/IABeattie/

Date: March 24, 2004

Ingrid A. Beattie, Reg. No. 42,306
Cynthia A. Kozakiewicz, Reg. No. 42,764
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.
One Financial Center
Boston, MA 02111
Telephone: (617) 542-6000
Customer No. 30623

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT
SEND TO:
BOX PROVISIONAL APPLICATION,
Assistant Commissioner for Patents, Washington, DC 20231

TRA 1900707v1

DESCRIPTION

COMPOSITIONS AND METHODS FOR TREATING PANCREATIC CANCER

Technical Field

The present invention relates to the field of biological science, more specifically to the field of cancer research. In particular, the present invention relates a composition comprising a small interfering RNA (siRNA) of PCDH1, CDH3, GPR107 or EphA4.

Background Art

Pancreatic ductal adenocarcinoma (PDACa) is the fifth leading cause of cancer death in the western world and has one of the highest mortality rates of any malignancy, with a 5-year survival rate only 4%. In USA, each year, estimated 30,700 patients are diagnosed with pancreatic cancer and nearly 30,000 will die of these diseases. The vast majority of patients are diagnosed at an advanced stage of disease at which it has no response to current therapies and the patients can survive for few months. Only surgical resection can offer the possibility of cure, but only 10-20% of patients with PDACa can undergo potentially curative resection and even after curative surgery, 80-90% of the patients relapse and die of the disease. Some improvements in surgical outcome or quality of life occur in patients who also receive chemotherapy including gemcitabine and/or radiation, although the impact on long-term survival has been minimal due to the intense resistance of PDACa to any treatment. At this point, management of most patients focuses on palliation.

Therefore, establishment of a novel molecular therapy for PDACa and identification of novel therapeutic molecular targets for PDACa are urgent issues for pancreatic cancer treatment now.

Disclosure of the Invention

The present invention based on the surprising discovery that small interfering RNAs (siRNAs) selective for PCDH1, CDH3, GPR107 or EphA4 are effective for

inhibiting the cellular growth of various cancer cells, including those involved in PDACa. The inventions described in this application are based in part on this discovery.

The invention provides methods for inhibiting cell growth. Among the methods provided are those comprising contacting a cell with a composition comprising a small interfering RNA (siRNA) of PCDH1, CDH3, GPR107 or EphA4. The invention also provides methods for inhibiting tumor cell growth in a subject. Such methods include administering to a subject a composition comprising a small interfering RNA (siRNA) of PCDH1, CDH3, GPR107 or EphA4. Another aspect of the invention provides methods for inhibiting the expression of the PCDH1, CDH3, GPR107 or EphA4 gene in a cell of a biological sample. Expression of the gene may be inhibited by introduction of a double stranded ribonucleic acid (RNA) molecule into the cell in an amount sufficient to inhibit expression of the PCDH1, CDH3, GPR107 or EphA4 gene. Another aspect of the invention relates to products including nucleic acid sequences and vectors as well as to compositions comprising them, useful, for example, in the provided methods. Among the products provided are siRNA molecules having the property to inhibit expression of the PCDH1, CDH3, GPR107 or EphA4 gene when introduced into a cell expressing said gene. Among such molecules are those that comprise a sense strand and an antisense strand, wherein the sense strand comprises a ribonucleotide sequence corresponding to a PCDH1, CDH3, GPR107 or EphA4 target sequence, and wherein the antisense strand comprises a ribonucleotide sequence which is complementary to said sense strand. The sense and the antisense strands of the molecule hybridize to each other to form a double-stranded molecule.

As used herein, the term "organism" refers to any living entity comprised of at least one cell. A living organism can be as simple as, for example, a single eukaryotic cell or as complex as a mammal, including a human being.

As used herein, the term "biological sample" refers to a whole organism or a subset of its tissues, cells or component parts (e.g. body fluids, including but not limited to blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). "Biological sample" further refers to a homogenate, lysate, extract, cell culture or tissue culture prepared from a whole organism or a subset of its cells, tissues or component parts, or a fraction or portion thereof. Lastly, "biological sample" refers to a medium, such as a nutrient broth or gel in which an

organism has been propagated, which contains cellular components, such as proteins or nucleic acid molecules.

The invention features methods of inhibiting cell growth. Cell growth is inhibited by contacting a cell with a composition of a small interfering RNA (siRNA) of PCDH1, CDH3, GPR107 or EphA4. The cell is further contacted with a transfection-enhancing agent. The cell is provided *in vitro*, *in vivo* or *ex vivo*. The subject is a mammal, *e.g.*, a human, non-human primate, mouse, rat, dog, cat, horse, or cow. The cell is a pancreatic ductal cell. Alternatively, the cell is a tumor cell (*i.e.*, cancer cell) such as a carcinoma cell or an adenocarcinoma cell. For example, the cell is a pancreatic ductal adenocarcinoma cell. By inhibiting cell growth is meant that the treated cell proliferates at a lower rate or has decreased viability than an untreated cell. Cell growth is measured by proliferation assays known in the art.

By the term "siRNA" is meant a double stranded RNA molecule which prevents translation of a target mRNA. Standard techniques of introducing siRNA into the cell are used, including those in which DNA is a template from which RNA is transcribed. The siRNA includes a sense PCDH1, CDH3, GPR107 or EphA4 nucleic acid sequence, an anti-sense PCDH1, CDH3, GPR107 or EphA4 nucleic acid sequence or both. The siRNA is constructed such that a single transcript has both the sense and complementary antisense sequences from the target gene, e.g., a hairpin.

The method is used to alter gene expression in a cell in which expression of PCDH1, CDH3, GPR107 or EphA4 is upregulated, e.g., as a result of malignant transformation of the cells. Binding of the siRNA to an PCDH1, CDH3, GPR107 or EphA4 transcript in the target cell results in a reduction in PCDH1, CDH3, GPR107 or EphA4 production by the cell. The length of the oligonucleotide is at least 10 nucleotides and may be as long as the naturally-occurring PCDH1, CDH3, GPR107 or EphA4 transcript. Preferably, the oligonucleotide is 19-25 nucleotides in length. Most preferably, the oligonucleotide is less than 75, 50 , or 25 nucleotides in length. Examples of siRNA oligonucleotides of PCDH1, CDH3, GPR107 or EphA4 which inhibit PCDH1, CDH3, GPR107 or EphA4 expression in mammalian cells include oligonucleotides containing target sequences, for example, nucleotides of SEQ ID NOs: 54, 57, 60 or 66, respectively.

Methods for designing double stranded RNA having the ability to inhibit gene expression in a target cell are known. (See for example, US Patent No. 6,506,559, herein

incorporated by reference in its entirety). For example, a computer program for designing siRNAs is available from the Ambion website (http://www.ambion.com/techlib/misc/siRNA_finder.html).

The computer program selects nucleotide sequences for siRNA synthesis based on the following protocol.

Selection of siRNA Target Sites

1. Beginning with the AUG start codon of the transcript, scan downstream for AA dinucleotide sequences. Record the occurrence of each AA and the 3' adjacent 19 nucleotides as potential siRNA target sites. Tuschl et al. recommend against designing siRNA to the 5' and 3' untranslated regions (UTRs) and regions near the start codon (within 75bases) as these may be richer in regulatory protein binding sites. UTR-binding proteins and/or translation initiation complexes may interfere with binding of the siRNA endonuclease complex.
2. Compare the potential target sites to the appropriate genome database (human, mouse, rat, etc.) and eliminate from consideration any target sequences with significant homology to other coding sequences. It is suggested to use BLAST, which can be found on the NCBI server at: www.ncbi.nlm.nih.gov/BLAST/
3. Select qualifying target sequences for synthesis. Selecting several target sequences along the length of the gene to evaluate is typical.

Also included in the invention are isolated nucleic acid molecules that include the nucleic acid sequence of target sequences, for example, nucleotides of SEQ ID NOs: 54, 57, 60 and 66 or a nucleic acid molecule that is complementary to the nucleic acid sequence of nucleotides of SEQ ID NOs: 54, 57, 60 and 66. As used herein, an "isolated nucleic acid" is a nucleic acid removed from its original environment (e.g., the natural environment if naturally occurring) and thus, synthetically altered from its natural state. In the present invention, isolated nucleic acid includes DNA, RNA, and derivatives thereof. When the isolated nucleic acid is RNA or derivatives thereof, base "t" shoulde be replaced with "u" in the nucleotide sequences. As used herein, the term "complementary" refers to Watson-Crick or Hoogsteen base pairing between nucleotides units of a nucleic acid molecule, and the term "binding" means the physical or chemical interaction between two polypeptides or compounds or associated polypeptides or compounds or combinations

thereof. Complementary nucleic acid sequences hybridize under appropriate conditions to form stable duplexes containing few or no mismatches. Furthermore, the sense strand and antisense strand of the isolated nucleotide of the present invention, can form double stranded nucleotide or hairpin loop structure by the hybridization. In a preferred embodiment, such duplexes contain no more than 1 mismatch for every 10 matches. In an especially preferred embodiment, where the strands of the duplex are fully complementary, such duplexes contain no mismatches. The nucleic acid molecule is less than 3581, 3205, 6840 or 3468 nucleotides in length for PCDH1, CDH3, GPR107 or EphA4, respectively. For example, the nucleic acid molecule is less than 500, 200, or 75 nucleotides in length. Also included in the invention is a vector containing one or more of the nucleic acids described herein, and a cell containing the vectors. The isolated nucleic acids of the present invention are useful for siRNA against PCDH1, CDH3, GPR107 or EphA4, or DNA encoding the siRNA. When the nucleic acids are used for siRNA or coding DNA thereof, the sense strand is preferably longer than 19 nucleotides, and more preferably longer than 21 nucleotides.

The invention is based in part on the discovery that the gene encoding PCDH1, CDH3, GPR107 or EphA4 is overexpressed in pancreatic ductal adenocarcinoma (PDACa) compared to non-cancerous pancreatic tissue. The cDNA of PCDH1, CDH3, GPR107 or EphA4 is 3581, 3205, 6840 or 3468 nucleotides in length. The nucleic acid and polypeptide sequences of PCDH1, CDH3, GPR107 or EphA4 are shown in SEQ ID NO: 1 and 2, 3 and 4, 5 and 6 or 7 and 8, respectively. The sequence data are also available via following accession numbers.

PCDH1(CFUPC): L11370, NM_002587

CDH3: X63629, AB046844

GPR107: NM_032925, (KIAA1624: R39794)

EphA4: L36645, NM_004438

Transfection of siRNAs comprising SEQ ID NOs: 54, 57, 60 and 66 resulted in a growth inhibition of PDACa cell lines. PCDH1 (CFUPC) belongs to the protocadherin family, the largest subgroup of cadherin superfamily of calcium-dependent cell-cell adhesion molecules. Many of the protocadherin are highly expressed in the central nervous system and they are likely to play roles in neuronal circuit development and the modulation of synaptic transmission (Sano K, Tanihara H, Heimark RL, Obata S,

Davidson M, St John T, Taketani S, Suzuki S. Protocadherins: a large family of cadherin-related molecules in central nervous system. *EMBO J.*, 12:2249-56, 1993.Frank M, and Kemler R. Protocadherins. *Curr Opin Cell Biol.*, 14:557-62, 2002). However, PCDH1 is abundant in pancreatic cancer cells, but not in central nervous system (Figure 3A), and its function remains unknown.

CDH3 is also a classical member of the cadherin family (Shimoyama Y, Yoshida T, Terada M, Shimosato Y, Abe O, Hirohashi S. Molecular cloning of a human Ca2+-dependent cell-cell adhesion molecule homologous to mouse placental cadherin: its low expression in human placental tissues. *J Cell Biol.*, 109:1787-94. 1989) and they link to catenins and cytoskeletons through its conserved intracellular domain, mediating signal-transduction that control cell polarity, differentiation, motility and cell growth (Christofori G. Changing neighbours, changing behaibour: cell adhesion molecules-mediated signaling during tumor progression. *EMBO J.*, 22, 2318-2323, 2003). However, different form E-cadherin or N-cadherin, the function of CDH3 still remains unclear. Its expression is observed in mammary glands and ovary, and loss of expression was reported in breast cancer and prostate cancer, although the expression of P-cadherin in breast cancer correlates with poor prognosis (Peralta Soler A, Knudsen KA, Salazar H, Han AC, Keshgegian AA. P-cadherin expression in breast carcinoma indicates poor survival. *Cancer*, 86:1263-1272. 1999).

GPR107 (KIAA1624) is one of the G protein-coupled receptors (GPCR) with seven transmembranes. A large percentage of today's prescription drugs target one or more GPCRs with most major therapeutic area being served to some extent by several GPCR-based drugs. Clearly, GPCRs are in the highest rank in the terms of drug discovery potential. GPR107 is expressed inrestrictedly in normal heart, placenta, skeletal muscle, prostate, testis, ovary, spinal cord as shown in Northern blot analysis (Figure 3C). This is not abundant in major vital organs, suggesting that targeting for these molecules would be expected to lead less toxicity in human body.

EphA4 is one of the receptor with tyrosine kinase activity and their functions with their ephrin ligands are best studies in the nervous system, where Eph receptors and ephrin molecules are involved in patterning the developing hindbrain, axon pathfinding and guiding neural crest cell migration (Dodelet VC, and Pasquale EB. Eph receptors and ephrin lignads: embryogenesis to tumorigenesis. *Oncogene*, 19: 5614-5619, 2000). These

molecules also regulate embryonic vascular development and there are some reports about the association of Eph/ephrin with tumor angiogenesis (Dodelet VC, and Pasquale EB. Eph receptors and ephrin lignads: embryogenesis to tumorigenesis. *Oncogene*, 19: 5614-5619, 2000). The Eph receptor family consists of 13 members and their ligands, ephrins, are divided into two subclasses, the A-subclass (A1-A5) and the B-subclass (B1-B3). The receptors are divided on the basis of sequence similarity and ligand affinity into A–subclass (EphA1-A8), and B-subclass (EphB1-B4, B6). A-type receptors typically bind to most or all A-type ligands, and B-type receptors bind to most or all B-type ligands, with the exception of EphA4 that can bind both A-type and most B-type ligands (Dodelet VC, and Pasquale EB. Eph receptors and ephrin lignads: embryogenesis to tumorigenesis. *Oncogene*, 19: 5614-5619, 2000).

Methods of inhibiting cell growth

The present invention relates to inhibiting cell growth, i.e, cancer cell growth by inhibiting expression of PCDH1, CDH3, GPR107 or EphA4. Expression of PCDH1, CDH3, GPR107 or EphA4 is inhibited by small interfering RNA (siRNA) that specifically target the PCDH1, CDH3, GPR107 or EphA4 gene. PCDH1, CDH3, GPR107 or EphA4 targets include, for example, nucleotides of SEQ ID NOs: 54, 57, 60 and 66.

In non-mammalian cells, double-stranded RNA (dsRNA) has been shown to exert a strong and specific silencing effect on gene expression, which is referred as RNA interference (RNAi) (1). dsRNA is processed into 20-23 nucleotides dsRNA called small interfering RNA (siRNA) by an enzyme containing RNase III motif. The siRNA specifically targets complementary mRNA with a multicomponent nuclease complex (2, 3). In mammalian cells, siRNA composed of 20 or 21-mer dsRNA with 19 complementary nucleotides and 3' terminal noncomplementary dimmers of thymidine or uridine, have been shown to have a gene specific knock-down effect without inducing global changes in gene expression (4). In addition, plasmids containing small nuclear RNA (snRNA) U6 or polymerase III H1-RNA promoter effectively produce such short RNA recruiting type III class of RNA polymerase III and thus can constitutively suppress its target mRNA (5, 6).

The growth of cells are inhibited by contacting a cell, with a composition containing a siRNA of PCDH1, CDH3, GPR107 or EphA4. The cell is further contacted with a transfection agent. Suitable transfection agents are known in the art. By inhibition

of cell growth is meant the cell proliferates at a lower rate or has decreased viability compared to a cell not exposed to the composition. Cell growth is measured by methods known in the art such as, the MTT cell proliferation assay.

The siRNA of PCDH1, CDH3, GPR107 or EphA4 is directed to a single target of PCDH1, CDH3, GPR107 or EphA4 gene sequence. Alternatively, the siRNA is directed to multiple target of PCDH1, CDH3, GPR107 or EphA4 gene sequences. For example, the composition contains siRNA of PCDH1, CDH3, GPR107 or EphA4 directed to two, three, four, or five or more target sequences of PCDH1, CDH3, GPR107 or EphA4. By PCDH1, CDH3, GPR107 or EphA4 target sequence is meant a nucleotide sequence that is identical to a portion of the PCDH1, CDH3, GPR107 or EphA4 gene. The target sequence can include the 5' untranslated (UT) region, the open reading frame (ORF) or the 3' untranslated region of the human PCDH1, CDH3, GPR107 or EphA4 gene. Alternatively, the siRNA is a nucleic acid sequence complementary to an upstream or downstream modulator of PCDH1, CDH3, GPR107 or EphA4 gene expression. Examples of upstream and downstream modulators include, a transcription factor that binds the PCDH1, CDH3, GPR107 or EphA4 gene promoter, a kinase or phosphatase that interacts with the PCDH1, CDH3, GPR107 or EphA4 polypeptide, a PCDH1, CDH3, GPR107 or EphA4 promoter or enhancer.

siRNA of PCDH1, CDH3, GPR107 or EphA4 which hybridize to target mRNA decrease or inhibit production of the PCDH1, CDH3, GPR107 or EphA4 polypeptide product encoded by the PCDH1, CDH3, GPR107 or EphA4 gene by associating with the normally single-stranded mRNA transcript, thereby interfering with translation and thus, expression of the protein. The siRNA is less than 500, 200, 100, 50, or 25 nucleotides in length. Preferably the siRNA is 19-25 nucleotides in length. Exemplary nucleic acid sequence for the production of PCDH1, CDH3, GPR107 or EphA4 siRNA include the sequences of nucleotides of SEQ ID NOs: 54, 57, 60 or 66 as the target sequence, respectively. Furthermore, in order to enhance the inhibition activity of the siRNA, nucleotide "u" can be added to 3'end of the antisense strand of the target sequence. The number of "u"s to be added is at least 2, generally 2 to 10, preferably 2 to 5. The added "u"s form single strand at the 3'end of the antisense strand of the siRNA.

The cell is any cell that expresses or over-expresses PCDH1, CDH3, GPR107 or EphA4. The cell is an epithelial cell such as a pancreatic ductal cell. Alternatively, the

cell is a tumor cell such as a carcinoma, adenocarcinoma, blastoma, leukemia, myeloma, or sarcoma. The cell is a pancreatic ductal adenocarcinoma.

An siRNA of PCDH1, CDH3, GPR107 or EphA4 is directly introduced into the cells in a form that is capable of binding to the mRNA transcripts. Alternatively, the DNA encoding the siRNA of PCDH1, CDH3, GPR107 or EphA4 is in a vector.

Vectors are produced for example by cloning a PCDH1, CDH3, GPR107 or EphA4 target sequence into an expression vector operatively-linked regulatory sequences flanking the PCDH1, CDH3, GPR107 or EphA4 sequence in a manner that allows for expression (by transcription of the DNA molecule) of both strands (Lee, N.S., Dohjima, T., Bauer, G., Li, H., Li, M.-J., Ehsani, A.,Salvaterra, P., and Rossi, J. (2002) Expression of small interfering RNAs targeted against HIV-1 rev transcripts in human cells. Nature Biotechnology 20 : 500-505.). An RNA molecule that is antisense to PCDH1, CDH3, GPR107 or EphA4 mRNA is transcribed by a first promoter (e.g., a promoter sequence 3' of the cloned DNA) and an RNA molecule that is the sense strand for the PCDH1, CDH3, GPR107 or EphA4 mRNA is transcribed by a second promoter (e.g., a promoter sequence 5' of the cloned DNA). The sense and antisense strands hybridize *in vivo* to generate siRNA constructs for silencing of the PCDH1, CDH3, GPR107 or EphA4 gene. Alternatively, two constructs are utilized to create the sense and anti-sense strands of a siRNA construct. Cloned PCDH1, CDH3, GPR107 or EphA4 can encode a construct having secondary structure, e.g., hairpins, wherein a single transcript has both the sense and complementary antisense sequences from the target gene.

A loop sequence consisting of an arbitrary nucleotide sequence can be located between the sense and antisense sequence in order to form the hairpin loop structure. Thus, the present invention also provides siRNA having the general formula 5'-[A]-[B]-[A']-3', wherein [A] is a ribonucleotide sequence corresponding to a sequence selected from the group consisting of nucleotides of SEQ ID NOs: 54, 57, 60 and 66,

[B] is a ribonucleotide sequence consisting of 3 to 23 nucleotides, and

[A'] is a ribonucleotide sequence consisting of the complementary sequence of [A]

The region [A] hybridizes to [A'], and then a loop consisting of region [B] is formed. The loop sequence may be preferably 3 to 23 nucleotide in length. The loop sequence, for example, can be selected from group consisting of following sequences (http://www.ambion.com/techlib/tb/tb_506.html). Furthermore, loop sequence consisting

of 23 nucleotides also provides active siRNA (Jacque, J.-M., Triques, K., and Stevenson, M. (2002) Modulation of HIV-1 replication by RNA interference. Nature 418 : 435-438.).

CCC, CCACC or CCACACC: Jacque, J. M., Triques, K., and Stevenson, M (2002) Modulation of HIV-1 replication by RNA interference. Nature, Vol. 418: 435-438.

UUCG: Lee, N.S., Dohjima, T., Bauer, G., Li, H., Li, M.-J., Ehsani, A., Salvaterra, P., and Rossi, J. (2002) Expression of small interfering RNAs targeted against HIV-1 rev transcripts in human cells. Nature Biotechnology 20 : 500-505. Fruscoloni, P., Zamboni, M., and Tocchini-Valentini, G. P. (2003) Exonucleolytic degradation of double-stranded RNA by an activity in Xenopus laevis germinal vesicles. Proc. Natl. Acad. Sci. USA 100(4): 1639-1644..

UUCAAGAGA: Dykxhoorn, D. M., Novina, C. D., and Sharp, P. A. (2002) Killing the messenger: Short RNAs that silence gene expression. Nature Reviews Molecular Cell Biology 4: 457-467.

For example, preferable siRNAs having hairpin loop structure of the present invention are shown below. In the following structure, the loop sequence can be selected from group consisting of CCC, UUCG, CCACC, CCACACC, and UUCAAGAGA. Preferable loop sequence is UUCAAGAGA ("ttcaagaga" in DNA).

GACAUCAAUGACAACACAC-[B]-GUGUGUUGUCAUUGAUGUC (for target sequence of SEQ ID NO:54)
GGAGACAGGCUGGUUGUUG-[B]-CAACAACCAGCCUGUCUCC (for target sequence of SEQ ID NO:57)
GUGGCUCUACCAGCUCCUG-[B]-CAGGAGCUGGUAGAGCCAC (for target sequence of SEQ ID NO:60)
GCAGCACCAUCAUCCAUUG-[B]-CAAUGGAUGAUGGUGCUGC (for target sequence of SEQ ID NO:66)

The regulatory sequences flanking the PCDH1, CDH3, GPR107 or EphA4 sequence are identical or are different, such that their expression can be modulated independently, or in a temporal or spatial manner. siRNAs are transcribed intracellularly

by cloning the PCDH1, CDH3, GPR107 or EphA4 gene templates into a vector containing, e.g., a RNA pol III transcription unit from the small nuclear RNA (snRNA) U6 or the human H1 RNA promoter. For introducing the vector into the cell, transfection-enhancing agent can be used. FuGENE (Rochediagnostices), Lipofectamin 2000 (Invitrogen), Oligofectamin (Invitrogen), and Nucleofactor (Wako pure Chemical) are useful as the transfection-enhancing agent.

Oligonucleotides and oligonucleotides complementary to various portions of PCDH1, CDH3, GPR107 or EphA4 mRNA were tested *in vitro* for their ability to decrease production of PCDH1, CDH3, GPR107 or EphA4 in tumor cells (e.g., using the pancreatic cell line such as pancreatic ductal adenocarcinoma(PDACa) cell line) according to standard methods. A reduction in PCDH1, CDH3, GPR107 or EphA4 gene product in cells contacted with the candidate siRNA composition compared to cells cultured in the absence of the candidate composition is detected using specific antibodies of PCDH1, CDH3, GPR107 or EphA4 or other detection strategies. Sequences which decrease production of PCDH1, CDH3, GPR107 or EphA4 in *in vitro* cell-based or cell-free assays are then tested for there inhibitory effects on cell growth. Sequences which inhibit cell growth *in vitro* cell-based assay are test *in vivo* in rats or mice to confirm decreased PCDH1, CDH3, GPR107 or EphA4 production and decreased tumor cell growth in animals with malignant neoplasms.

Methods of treating malignant tumors

Patients with tumors characterized as over-expressing PCDH1, CDH3, GPR107 or EphA4 are treated by administering siRNA of PCDH1, CDH3, GPR107 or EphA4. siRNA therapy is used to inhibit expression of PCDH1, CDH3, GPR107 or EphA4 in patients suffering from or at risk of developing, for example, pancreatic ductal adenocarcinoma (PDACa). Such patients are identified by standard methods of the particular tumor type. Pancreatic ductal adenocarcinoma (PDACa) is diagnosed for example, by CT, MRI, ERCP, MRCP, computer tomography, or ultrasound. Treatment is efficacious if the treatment leads to clinical benefit such as, a reduction in expression of PCDH1, CDH3, GPR107 or EphA4, or a decrease in size, prevalence, or metastatic potential of the tumor in the subject. When treatment is applied prophylactically, "efficacious" means that the treatment retards or prevents tumors from forming or prevents or alleviates a symptom of clinical symptom.

of the tumor. Efficaciousness is determined in association with any known method for diagnosing or treating the particular tumor type.

siRNA therapy is carried out by administering to a patient a siRNA by standard vectors and/or gene delivery systems. Suitable gene delivery systems may include liposomes, receptor-mediated delivery systems, or viral vectors such as herpes viruses, retroviruses, adenoviruses and adeno-associated viruses, among others. A therapeutic nucleic acid composition is formulated in a pharmaceutically acceptable carrier. The therapeutic composition may also include a gene delivery system as described above. Pharmaceutically acceptable carriers are biologically compatible vehicles which are suitable for administration to an animal, e.g., physiological saline. A therapeutically effective amount of a compound is an amount which is capable of producing a medically desirable result such as reduced production of a PCDH1, CDH3, GPR107 or EphA4 gene product, reduction of cell growth, e.g., proliferation, or a reduction in tumor growth in a treated animal.

Parenteral administration, such as intravenous, subcutaneous, intramuscular, and intraperitoneal delivery routes, may be used to deliver siRNA compositions of PCDH1, CDH3, GPR107 or EphA4. For treatment of pancreatic tumors, direct infusion the celiac artery, splenic artery, or common hepatic artery, is useful.

Dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular nucleic acid to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Dosage for intravenous administration of nucleic acids is from approximately 10^6 to 10^{22} copies of the nucleic acid molecule.

The polynucleotides are administered by standard methods, such as by injection into the interstitial space of tissues such as muscles or skin, introduction into the circulation or into body cavities or by inhalation or insufflation. Polynucleotides are injected or otherwise delivered to the animal with a pharmaceutically acceptable liquid carrier, e.g., a liquid carrier, which is aqueous or partly aqueous. The polynucleotides are associated with a liposome (e.g., a cationic or anionic liposome). The polynucleotide includes genetic information necessary for expression by a target cell, such as a promoters.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this

invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Brief Description of the Drawings

Figure 1 depicts photographs showing the results of validation of over expression of PCDH1 (A) and CDH3 (B) in the PDACa cells by RT-PCR. The microdissected normal pancreatic ductal epithelial cells (Normal) and vital organs (lung, heart, liver, kidney and bone marrow) form the same individual were compared by semiquantitative RT-PCR.

Figure 2 depicts photographs showing the result of immunohistochemistry in PDACa tissues. Overexpression of CDH3 and EphA4 protein was observed in pancreatic ductal adenocarcinoma, but not in normal pancreatic duct.

Figure 3 depicts photographs of Northern blot analysis showing the expression pattern in normal adult tissues of each target genes for pancreatic cancer. (A) PCDH1, (B) CDH3, (C) GPR107, and (D) EphA4.

Figure 4 depicts photographs showing the effect of Knocking-down endogenous PCDH1 in PDACa cell, PK-45P, by siRNA. Figure 4 (A) shows the results of RT-PCR. It validated knockdown effect of PCDH1 mRNA by transfection of siRNA expression vectors 410si, but not by 3344si, 3498si and EGFPsi. The 410si, 3344si, and 3498si were designed specifically for PCDH mRNA sequence, and EGFP was for EGFP mRNA sequence. RNA was harvested 48 hours after transfection and analyzed. ACTB was used to normalize input cDNA. Figure 4 (B) is a photograph showing the results of Colony formation assay. It showed drastic decrease of colony numbers in the cells one week after transfection with 410si that was validated to knock down PCDH1 effectively by RT-PCR. Figure 4 (C) is a photograph showing the results MTT assay. It also showed drastic decreased number of the grown cells transfected with 410si but not by 3344si, 3498si and EGFPsi.

Figure 5 depicts photographs showing the effect of Knocking-down endogenous CDH3 in PDACa cell, KLM-1, by siRNA. Figure 5 (A) shows the results of RT-PCR. It validated knockdown effect of CDH3 mRNA by transfection of siRNA expression vectors si24 but not by si29, si70 and EGFPsi. The si24, si29, and si70 were designed specifically for CDH3 mRNA sequence, and EGFPsi was for EGFP mRNA sequence. RNA was harvested 48 hours after transfection and analyzed. ACTB was used to normalize input cDNA. Figure 5 (B) is a photograph showing the results of Colony formation assay. It showed drastic decrease of colony numbers in the cells one week after transfection with si24 that was validated to knock down CDH3 effectively by RT-PCR. Figure 5 (C) is a photograph showing the results MTT assay. It also showed drastic decreased number of the grown cells transfected with si24, but not by si29, si70 and EGFPsi.

Figure 6 depicts photographs showing the effect of Knocking-down endogenous GPR107 in PDACa cell, KLM-1, by siRNA. Figure 6 (A) shows the results of RT-PCR. It validated knockdown effect of GPR107 mRNA by transfection of siRNA expression vectors 1003si, but not by 1066si, 1118si, 1171si and EGFPsi. The 1003si, 1066si, 1118si, and 1171si were designed specifically for GPR107 mRNA sequence, and EGFPsi was for EGFP mRNA sequence. RNA was harvested 48 hours after transfection and analyzed. ACTB was used to normalize input cDNA. Figure 6 (B) is a photograph showing the results of Colony formation assay. It showed decrease of colony numbers in the cells one week after transfection with 1003si that was validated to knock down GPR107 effectively by RT-PCR. Figure 6 (C) is a photograph showing the results MTT assay. It also showed decreased number of the grown cells transfected with 1003si, but not by1118si, 1171si and EGFPsi.

Figure 7 depicts photographs showing the effect of Knocking-down endogenous EphA4 in PDACa cell, MIA-Paca2, by siRNA. Figure 7 (A) shows the results of RT-PCR. It validated knockdown effect of EphA4 mRNA by transfection of siRNA expression vectors 1313si, but not by 198si, 468si and EGFPsi. The 198si, 468si, 1313si were designed specifically for EphA4 mRNA sequence, and EGFPsi was for EGFP mRNA sequence. RNA was harvested 48 hours after transfection and analyzed. ACTB was used to normalize

input cDNA. Figure 7 (B) is a photograph showing the results of Colony formation assay. It showed drastic decrease of colony numbers in the cells one week after transfection with 1313si that was validated to knock down EphA4 effectively by RT-PCR. Figure 7 (C) is a photograph showing the results MTT assay. It also showed drastic decreased number of the grown cells transfected with1313si, but not by 198si, 468si and EGFPsi.

Best Mode for Carrying out the Invention

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

[Example 1] General Methods

Cell lines and tissue specimens

Human Pancreatic cell lines PK45P, KLM1 and MIA-PaCa2 (ATCC Number: CRL-1420) were obtained from the Cell Resource Center for Biomedical Research, Institute of Development, Aging and Cancer, Tohoku University. All these cells are publicly available.

Isolation of over-expressing genes in PDACa cells by using cDNA microarray

Fabrication of the cDNA microarray slides has been described (Ono K, Tanaka T, Tsunoda T, Kitahara O, Kihara C, Okamoto A, Ochiai K, Takagi T, and Nakamura Y. *Cancer Res.*, 60: 5007-5011, 2000). For each analysis of expression profiles it was prepared duplicate sets of cDNA microarray slides containing approximately 27,000 DNA spots, to reduce experimental fluctuation. Briefly, total RNA was purified from PDACa cells and normal pancreatic duct epithelium microdissected from 18 pancreatic cancer tissues. T7-based RNA amplification was carried out to obtain adequate RNA for microarray experiments. Aliquots of amplified RNA from PDACa cells and normal duct epithelium were labeled by reverse transcription with Cy5-dCTP and Cy3-dCTP, respectively (Amersham Biosciences). Hybridization, washing, and detection were carried out as described previously (Ono K, Tanaka T, Tsunoda T, Kitahara O, Kihara C, Okamoto A, Ochiai K, Takagi T, and Nakamura Y. *Cancer Res.*, 60: 5007-5011, 2000). Subsequently, among the up-regulated genes, it was focused four genes, PCDH1, CDH3, GPR107 and EphA4 because its expression ratio was greater than 5.0 in more than 50% of

informative cancers and their expression level in normal vital major organs was relatively low according to the our previous data of gene expression in 29 normal human tissues (Saito-Hisaminato A, Katagiri T, Kakiuchi S, Nakamura T, Tsunoda T, Nakamura Y. Genome-wide profiling of gene expression in 29 normal human tissues with a cDNA microarray. *DNA Res.*, 9: 35-45, 2002).

Semiquantitative RT-PCR for PCDH1, CDH3, GPR107 and EphA4

RNA from the microdissected PDACa cells and normal pancreatic ductal epithelial cells were subject to two-round amplification by T7-based *in vitro* transcription (Epicentre Technologies) and synthesized to single-strand cDNA. It was prepared appropriate dilutions of each single-stranded cDNA for subsequent PCR amplification by monitoring β-actin (ACTB) as a quantitative control. The primer sequences the present inventors used were 5'-AGAAGGAGACCAAGGACCTGTAT-3' (SEQ.ID.NO.9) and 5'-AGAACTTTATTGTCAGGGTCAAGG-3' (SEQ.ID.NO.10) for PCDH1, 5'-CTGAAGGCGGCTAACACAGAC-3' (SEQ.ID.NO.11) and 5'-TACACGATTGTCCTCACCCTTC-3' (SEQ.ID.NO.12) for CDH3, and 5'-CATCCACGAAACTACCTTCAACT-3' (SEQ.ID.NO.13) and 5'-TCTCCTTAGAGAGAAGTGGGGTG-3' (SEQ.ID.NO.14) for ACTB. All reactions involved initial denaturation at 94°C for 2 min followed by 21 cycles (for ACTB) or 28-32 cycles (for PCDH1 and CDH3) at 94°C for 30 s, 58°C for 30 s, and 72°C for 1 min, on a GeneAmp PCR system 9700 (PE Applied Biosystems).

Immunohistochemistry

Formalin-fixed and paraffin-embedded PDACa sections were immunostained using a mouse anti-CDH3 monoclonal antibody (BD Transduction Laboratories) or a rabbit anti-EPHA4 (EphA4) polyclonal antibody (Santa Cruz Biotechnology) for CDH3 and EPHA4 expression. Deparaffinized tissue sections were placed in 10 mM citrate buffer, pH 6.0, and heated to 108°C in an autoclave for 15 minutes for antigen retrieval. Sections were incubated with a 1:10 dilution or a 1:100 dilution of primary antibody for CDH3 or EPHA4, respectively, in a humidity chamber for an hour at room temperature, and developed with peroxidase labeled-dextran polymer followed by diaminobenzidine

(DAKO Envision Plus System; DAKO Corporation, Carpinteria, CA). Sections were counterstained with hematoxylin. For negative controls, primary antibody was omitted.

Northern blot analysis

Human multiple-tissue Northern blots (Clontech) were hybridized with a [α^{-32}P] dCTP-labeled PCR product amplified by the primers described above. Pre-hybridization, hybridization and washing were performed according to the supplier's recommendations. The blots were auto-radiographed with intensifying screens at -80°C for 5 days.

Construction of psiU6BX Plasmid

The DNA flagment encoding siRNA was inserted into the GAP at nucleotide 485-490 as indicated (-) in the following plasmid sequence (SEQ ID No: 67).

GACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTACAATCTGCTCTGGAT
CCACTAGTAACGGCCGCCAGTGTGCTGGAATTCGGCTTGGGGATCAGCGTTTGAGTAAGA
GCCCGCGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAAAGACGCGCAGGCAAAACG
CACCACGTGACGGAGCGTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGAAGAGGG
CCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGATAAT
TAGAATTAATTTGACTGTAAACACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTA
ATAATTTCTTGGGTAGTTTGCAGTTTTAAAATTATGTTTTAAAATGGACTATCATATGCT
TACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAA
CACC------TTTTTACATCAGGTTGTTTTTCTGTTTGGTTTTTTTTTTACACCACGTTT
ATACGCCGGTGCACGGTTTACCACTGAAAACACCTTTCATCTACAGGTGATATCTTTTAA
CACAAATAAAATGTAGTAGTCCTAGGAGACGGAATAGAAGGAGGTGGGGCCTAAAGCCGA
ATTCTGCAGATATCCATCACACTGGCGGCCGCTCGAGTGAGGCGGAAAGAACCAGCTGGG
GCTCTAGGGGGTATCCCCACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGG
TTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCT
TCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCC
CTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTAGGGTG
ATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGT
CCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGG
TCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGC
TGATTTAACAAAAATTTAACGCGAATTAATTCTGTGGAATGTGTGTCAGTTAGGGTGTGG
AAAGTCCCCAGGCTCCCCAGCAGGCAGAAGTATGCAAAGCATGCATCTCAATTAGTCAGC
AACCAGGTGTGGAAAGTCCCCAGGCTCCCCAGCAGGCAGAAGTATGCAAAGCATGCATCT
CAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCC
CAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGA

GGCCGCCTCTGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGG
CTTTTGCAAAAAGCTCCCGGGAGCTTGTATATCCATTTTCGGATCTGATCAAGAGACAGG
ATGAGGATCGTTTCGCATGATTGAACAAGATGGATTGCACGCAGGTTCTCCGGCCGCTTG
GGTGGAGAGGCTATTCGGCTATGACTGGGCACAACAGACAATCGGCTGCTCTGATGCCGC
CGTGTTCCGGCTGTCAGCGCAGGGGCGCCCGGTTCTTTTTGTCAAGACCGACCTGTCCGG
TGCCCTGAATGAACTGCAGGACGAGGCAGCGCGGCTATCGTGGCTGGCCACGACGGGCGT
TCCTTGCGCAGCTGTGCTCGACGTTGTCACTGAAGCGGGAAGGGACTGGCTGCTATTGGG
CGAAGTGCCGGGGCAGGATCTCCTGTCATCTCACCTTGCTCCTGCCGAGAAAGTATCCAT
CATGGCTGATGCAATGCGGCGGCTGCATACGCTTGATCCGGCTACCTGCCCATTCGACCA
CCAAGCGAAACATCGCATCGAGCGAGCACGTACTCGGATGGAAGCCGGTCTTGTCGATCA
GGATGATCTGGACGAAGAGCATCAGGGGCTCGCGCCAGCCGAACTGTTCGCCAGGCTCAA
GGCGCGCATGCCCGACGGCGAGGATCTCGTCGTGACCCATGGCGATGCCTGCTTGCCGAA
TATCATGGTGGAAAATGGCCGCTTTTCTGGATTCATCGACTGTGGCCGGCTGGGTGTGGC
GGACCGCTATCAGGACATAGCGTTGGCTACCCGTGATATTGCTGAAGAGCTTGGCGGCGA
ATGGGCTGACCGCTTCCTCGTGCTTTACGGTATCGCCGCTCCCGATTCGCAGCGCATCGC
CTTCTATCGCCTTCTTGACGAGTTCTTCTGAGCGGGACTCTGGGGTTCGAAATGACCGAC
CAAGCGACGCCCAACCTGCCATCACGAGATTTCGATTCCACCGCCGCCTTCTATGAAAGG
TTGGGCTTCGGAATCGTTTTCCGGGACGCCGGCTGGATGATCCTCCAGCGCGGGGATCTC
ATGCTGGAGTTCTTCGCCCACCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAATAA
AGCAATAGCATCACAAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGGT
TTGTCCAAACTCATCAATGTATCTTATCATGTCTGTATACCGTCGACCTCTAGCTAGAGC
TTGGCGTAATCATGGTCATAGCTGTTTCCTGTGTGAAATTGTTATCCGCTCACAATTCCA
CACAACATACGAGCCGGAAGCATAAAGTGTAAAGCCTGGGGTGCCTAATGAGTGAGCTAA
CTCACATTAATTGCGTTGCGCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGCCAG
CTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCC
GCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCT
CACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATG
TGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTC
CATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGA
AACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCT
CCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTG
GCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAG
CTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTAT
CGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAAC
AGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAAC
TACGGCTACACTAGAAGAACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTC
GGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTTTTTTT
GTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTT
TCTACGGGGTCTGACGCTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGA

TTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATC
TAAAGTATATATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCT
ATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATA
ACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCA
CGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGCGCAGA
AGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGCTAGA
GTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGCATCGTG
GTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGCGA
GTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTT
GTCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCT
CTTACTGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCA
TTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAAT
ACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGA
AAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCC
AACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGG
CAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCATACTCTTC
CTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTT
GAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCA
CCTGACGTC

snRNA U6 gene is reported to be transcribed by RNA polymerase III, which produce short transcripts with uridines at the 3' end. The genomic fragment of the snRNA U6 gene containing the promoter region was amplified by PCR using a set of primers,

5'-GGGGATCAGCGTTTGAGTAA-3' (SEQ ID No: 68), and

5'-TAGGCCCCACCTCCTTCTAT-3' (SEQ ID No: 69) and human placental DNA as a template. The product was purified and cloned into pCR plasmid vector using a TA cloning kit according to the supplier's protocol (Invitrogen). The *Bam*HI, *Xho*I fragment containing the snRNA U6 gene was purified and cloned into nucleotide 1257 to 56 fragment of pcDNA3.1(+) plasmid, which was amplified by PCR with a set of primer,

5'-TGCGGATCCAGAGCAGATTGTACTGAGAGT-3' (SEQ ID No: 70) and

5'- CTCTATCTCGAGTGAGGCGGAAAGAACCA-3' (SEQ ID No: 71). The ligated DNA was used for a template of PCR with primers,

5'-TTTAAGCTTGAAGACTATTTTTACATCAGGTTGTTTTTCT-3' (SEQ ID No: 72) and

5'-TTTAAGCTTGAAGACACGGTGTTTCGTCCTTTCCACA-3' (SEQ ID No: 73). The product was digested with HindIII, which was subsequently self-ligated to produce psiU6BX vector plasmid. For the control, psiU6BX-EGFP was prepared by cloning double-stranded oligonucleotides of

5'- CACCGAAGCAGCACGACTTCTTCTTCAAGAGAGAAGAAGTCGTGCT GCTTC-3' (SEQ ID No: 74) and

5'- AAAAGAAGCAGCACGACTTCTTCTCTCTTGAAGAAGAAGTCGTGCT GCTTC -3' (SEQ ID No: 75) into the BbsI site in the psiU6BX vector.

siRNA-expressing constructs

The nucleotide sequence of the siRNAs were designed using an siRNA design computer program available from the Ambion website. (http://www.ambion.com/techlib/misc/siRNA_finder.html). Briefly, nucleotide sequences for siRNA synthesis are selected using the following protocol.

Selection of siRNA Target Sites:

1. Starting with the AUG start codon of the each gene transcript, scan downstream for an AA dinucleotide sequences. The occurrence of each AA and the 3' adjacent 19 nucleotides are recorded as potential siRNA target sites. Tuschl et al. recommend against designing siRNA to the 5' and 3' untranslated regions (UTRs) and regions near the start codon (within 75bases) as these may be richer in regulatory protein binding sites. UTR-binding proteins and/or translation initiation complexes may interfere with binding of the siRNA endonuclease complex.

2. The potential target sites are compared to the appropriate genome database (human, mouse, rat, etc.) to eliminate target sequences with significant homology to other coding sequences.

3. Qualifying target sequences are selected for synthesis. Several target sequences along the length of the gene are selected for evaluation.

The oligonucleotides used for siRNAs of PCDH1, CDH3, GPR107 or EphA4 are shown below. Each oligionucleotide is a combination of a sense nucleotide sequence and an antisense nucleotide sequence of the target sequence. The nucleotide sequences of the hairpin loop structure and target sequence are shown in SEQ ID NO:54 to SEQ ID NO:57

and SEQ ID NO:60 to SEQ ID NO:66, respectively (endonuclease recognition cites are eliminated from each hairpin loop structure sequence).

Insert sequence of siRNA for PCDH1

410si:

5'-CACCGACATCAATGACAACACACTTCAAGAGAGTGTGTTGTCATTGATGTC-3' (SEQ ID NO: 15) and

5'-AAAAGACATCAATGACAACACACTCTCTTGAAGTGTGTTGTCATTGATGTC-3' (SEQ ID NO:16)

3344si:

5'-CACCGTCTACTCCAAACCTAGGTTTCAAGAGAACCTAGGTTTGGAGTAGAC-3' (SEQ ID NO: 17) and

5'-AAAAGTCTACTCCAAACCTAGGTTCTCTTGAAACCTAGGTTTGGAGTAGAC-3' (SEQ ID NO: 18)

3498siRNA:

5'-CACCCCTCTTCCTCACCACTAGGTTCAAGAGACCTAGTGGTGAGGAAGAGG-3' (SEQ ID NO: 19) and

5'-AAAACCTCTTCCTCACCACTAGGTCTCTTGAACCTAGTGGTGAGGAAGAGG-3' (SEQ ID NO: 20)

Insert sequence of siRNA for CDH3

si24:

5'-CACCGGAGACAGGCTGGTTGTTGTTCAAGAGACAACAACCAGCCTGTCTCC-3' (SEQ ID NO: 21)and

5'-AAAAGGAGACAGGCTGGTTGTTGTCTCTTGAACAACAACCAGCCTGTCTCC-3' (SEQ ID NO: 22)

si29:

5'-CACCCATCTCCATCATCGTGACCTTCAAGAGAGGTCACGATGATGGAGATG-3' (SEQ ID NO: 23)and

5'-AAAACATCTCCATCATCGTGACCTCTCTTGAAGGTCACGATGATGGAGATG-3' (SEQ ID NO: 24)

si70:

5'-CACCCATCACGGACAAGGACCTGTTCAAGAGACAGGTCCTTGTCCGTGATG-3' (SEQ ID NO: 25)and

5'-AAAACATCACGGACAAGGACCTGTCTCTTGAACAGGTCCTTGTCCGTGATG-3' (SEQ ID NO: 26)

Insert sequence of siRNA for GPR107

1003si:

5'-CACCGTGGCTCTACCAGCTCCTGTTCAAGAGACAGGAGCTGGTAGAGCCAC-3' (SEQ ID NO: 27)and

5'-AAAAGTGGCTCTACCAGCTCCTGTCTCTTGAACAGGAGCTGGTAGAGCCAC-3' (SEQ ID NO: 28)

1066si:

5'-CACCATTCCGTCCGGCTTCAGATTTCAAGAGAATCTGAAGCCGGACGGAAT-3' (SEQ ID NO: 29)and

5'-AAAAATTCCGTCCGGCTTCAGATTCTCTTGAAATCTGAAGCCGGACGGAAT-3' (SEQ ID NO: 30)

1118si:

5'-CACCGACTTGGAAATGGAGTCCGTTCAAGAGACGGACTCCATTTCCAAGTC-3' (SEQ ID NO: 31)and

5'-AAAAGACTTGGAAATGGAGTCCGTCTCTTGAACGGACTCCATTTCCAAGTC-3' (SEQ ID NO: 32)

1171si:

5'-CACCGAAAGTCAAGAAGGTGACCTTCAAGAGAGGTCACCTTCTTGACTTTC-3' (SEQ ID NO: 33) and

5'-AAAAGAAAGTCAAGAAGGTGACCTCTCTTGAAGGTCACCTTCTTGACTTTC-3' (SEQ ID NO: 34)

Insert sequence of siRNA for EphA4

198si:

5'-CACCTCCGAACCTACCAAGTGTGTTCAAGAGACACACTTGGTAGGTTCGGA-3' (SEQ ID NO: 35)and

5'-AAAATCCGAACCTACCAAGTGTGTCTCTTGAACACACTTGGTAGGTTCGGA-3' (SEQ ID NO: 36)

468si:

5'-CACCTCATGAAGCTGAACACCGATTCAAGAGATCGGTGTTCAGCTTCATGA-3' (SEQ ID NO: 37)and

5'-AAAATCATGAAGCTGAACACCGATCTCTTGAATCGGTGTTCAGCTTCATGA-3' (SEQ ID NO: 38)

1313si:

5'-CACCGCAGCACCATCATCCATTGTTCAAGAGACAATGGATGATGGTGCTGC-3' (SEQ ID NO: 39) and

5'-AAAAGCAGCACCATCATCCATTGTCTCTTGAACAATGGATGATGGTGCTGC-3' (SEQ ID NO: 40)

Insert sequence of siRNA for control

EGFPsi: (control)

5'- CACCGAAGCAGCACGACTTCTTCTTCAAGAGAGAAGAAGTCGTGCTGCTTC -3' (SEQ ID NO: 74) and

5'-AAAAGAAGCAGCACGACTTCTTCTCTCTTGAAGAAGAAGTCGTGCTGCTTC-3' (SEQ ID NO: 75)

Sequence ID NO of each sequences are listed in Table1

gene	siRNA	effect	insert seq SEQ ID NO		hairpin siRNA	target SEQ ID NO	position
PCDH1	410si	+	15	16	41	54	595-613
PCDH1	3344si	-	17	18	42	55	3565-3583
PCDH1	3498si	-	19	20	43	56	3719-3737
CDH3	si24	+	21	22	44	57	556-574
CDH3	si29	-	23	24	45	58	670-688
CDH3	si70	-	25	26	46	59	1768-1786
GPR107	1003si	+	27	28	47	60	1570-1588
GPR107	1066si	-	29	30	48	61	1633-1651
GPR107	1118si	-	31	32	49	62	1685-1703
GPR107	1171si	-	33	34	50	63	1738-1756
EphA4	198si	-	35	36	51	64	242-260
EphA4	468si	-	37	38	52	65	530-548
EphA4	1313si	+	39	40	53	66	1357-1375
control	EGFPsi	-	74	75			

colony formation / MTT assay

Human PDACa cell lines among PK45P, KLM1 and MIA-PaCa2, were plated onto 10-cm dishes (5 X 10^5 cells/dish) and transfected with psiU6BX containing EGFP target sequence (EGFP) and psiU6BX containing target sequence using Lipofectamine 2000 (Invitrogen) or FuGENE6 (Roche), according to manufacture's instruction. Cells were selected by 500 mg/ml Geneticin for one week, and preliminary cells were harvested 48 hours after transfection and analyzed by RT-PCR to validate knockdown effect on PCDH1, CDH3, GPR107 and EphA4. The primers of RT-PCR were the same ones described above. These cells were also stained by Giemsa solution and performed MTT assay to evaluate the colony formation and the cell number, respectively.

[Example 2] Reduction of the expression of the genes PCDH1, CDH3, GPR107 or EphA4 and growth suppression of cancer cells by siRNA

In previous study, it was generated precise expression profiles of PDACa by combining laser microdissection with genome-wide cDNA microarrays with 27,000 genes spotted. The present inventors identified more than 200 genes as up-regulated genes in PDACa cells comparing with the expression pattern of normal pancreatic ductal epithelium that was thought to be the origin of PDACa (Nakamura T, Furukawa Y, Nakagawa H,

Tsunoda T, Ohigashi H, Murata K, Ishikawa O, Ohgaki, Kashimura N, Miyamoto M, Hirano S, Kondo S, Katoh H, Nakamura Y, and Katagiri T. Genome-wide cDNA microarray analysis of gene-expression profiles in pancreatic cancers using populations of tumor cells and normal ductal epithelium cells selected for purity by laser microdissection. *Oncogene*, 2004 Feb 9, Epub ahead of print). Based on these expression profile of PDACa cells, the present inventors selected four over-expressing genes, PCDH1 and CDH3 and validated their overexpression in PDACa by RT-PCR using the cDNA from microdissected PDACa cells (Figure 1A,B) or immunohistochemistry (Figure 2). Their products are supposed to be cell–surface membrane proteins that are ideal molecule target for drug design and antibody therapy against cancer. Clinical trials approved that Trastuzumab (Herceptin), a humanized monoclonal antibody against ERBB2 (Her2) is effective for subsets of metastatic breast cancer with HER2 over-expressed, and cell-surface molecules that mediates signaling process necessary for essential cellular functions and for maintaining the malignant phenotypes are now most promising targets for cancer therapy (Pegram M, and Slamon DJ. Biological rationale for Her2/neu as a target for monoclonal antibody therapy. *Semin.Oncology*, 27 (suppl 9): 13-19, 2000). Drug design targeting these membrane molecules can be approached both by blocking their growth-promoting signals and/or by modulating ADCC activity in the same way with Trastuzumab.

(1) PCDH1 (Protocadherin 1) (Genbank Accession No.NM_002587; SEQ ID No.1,2)

To investigate the growth or survival effect of PCDH1 on PDACa cells, the present inventors knocked down their endogenous expression of PCDH1 specifically by mammalian vector-based RNA interference (RNAi) technique in PDACa cell line. PCDH1 is expressed inrestrictedly in normal heart, placenta, prostate as shown in Northern blot analysis (Figure 3A). This is not abundant in major vital organs, suggesting that targeting for these molecules would be expected to lead less toxicity in human body.

The transfection of the siRNA-producing vectors clearly resulted in reduction of the endogenous expression in one designed siRNA, 410si, for PCDH1 (Figure 4A). This knocking-down effect by the siRNA on PCDH1 mRNA resulted in drastic growth suppression in colony formation assay (Figure 4B) and MTT assay (Figure 4C). These findings strongly suggested that overexpression of PCDH1 in PDACa cells were associated with cancer cell viability. PCDH1 and other protocadherins are supported to have homophilic interaction on the cell surface by means of their cadherin domains and

modulate intercellular signal transduction for cytoskeleton conformation, cell motility or cell growth (Sano K, Tanihara H, Heimark RL, Obata S, Davidson M, St John T, Taketani S, Suzuki S. Protocadherins: a large family of cadherin-related molecules in central nervous system. *EMBO J.*, 12:2249-56, 1993, Frank M, and Kemler R. Protocadherins. *Curr Opin Cell Biol.*, 14:557-62, 2002.). According to our data, PCDH1 is likely to modulate positive signal for pancreatic cancer cell growth through its homophilic interaction in cell-cell adhesion.

(2) CDH3 (P-cadherin) (Genbank Accession No.NM_001793; SEQ ID No.3,4)

The present inventors validated CDH3 overexpression in PDACa cells by RT-PCR (Figure 1B) and immunohistochemistry (Figure 2A), and according to the microarray data and RT-PCR (Figure 1B), CDH3 overexpression was one of the most predominant patterns among more than 200 up-regulated genes in our PDACa profiles. CDH3 is expressed inrestrictedly in normal thymus, prostate, ovary, trachea as shown in Northern blot analysis (Figure 3B). This is not abundant in major vital organs, suggesting that targeting for these molecules would be expected to lead less toxicity in human body.

To investigate the growth or survival effect of CDH3 on PDACa cells, the present inventors knocked down their endogenous expression of CDH3 specifically by mammalian vector-based RNA interference (RNAi) technique in PDACa cell line. The transfection of the siRNA-producing vectors clearly resulted in reduction of the endogenous expression in one designed siRNA, si24, for CDH3 (Figure 5A). This knocking-down effect by the siRNA on CDH3 mRNA resulted in drastic growth suppression in colony formation assay (Figure 5B) and MTT assay (Figure 5C). These findings strongly suggested that overexpression of CDH3 in PDACa cells were associated with cancer cell viability as well as cell-cell interaction, and this molecule may involve signal transduction from cell-cell interaction. PDACa is extremely aggressive and high expression of CDH3 in PDACa may be associated with their aggressiveness and metastatic potential as well.

(3) GPR107 (G protein-coupled receptor 107) (Genbank Accession No. AB046844; SEQ ID No.5,6)

The present inventors identified this orphan GPCR as a target for pancreas cancer, which function and ligands are unknown. To investigate the growth or survival effect of GPR107 on PDACa cells, the present inventors knocked down their endogenous expression of GPR107 specifically by siRNA in PDACa cell line. The transfection of the

siRNA-producing vectors clearly resulted in reduction of the endogenous expression in one designed siRNA, 1003si, for GPR107 (Figure 6A). This knocking-down effect by the siRNA on GPR107 mRNA resulted in growth suppression in colony formation assay (Figure 6B) and MTT assay (Figure 6C). These findings strongly suggested that overexpression of GPR107 in PDACa cells were associated with cancer cell viability. Hence, these findings suggested that blocking by antibody or antagonist for GPR107 is a promising approach for PDACa treatment.

(4) EphA4 (Genbank Accession No.NM_004438; SEQ ID No.7,8)

The present inventors validated EphA4 overexpression in PDACa by RT-PCR and immunohistochemistry (Figure 2B), but in pancreatic cancer tissues, the ligand of EphA4 is unknown. Northern blot analysis (Figure 3D) showed that EphA4 was abundant in testis, not in central nervous system and other major organs. Recently the antibody targeting against other Eph receptor family member, EphA2 that is also over-expressed in several cancers, was reported to inhibit breast cancer cell growth *in vitro* and *in vivo* (Carles-Kinch K, Kilpatrick KE, Stewart JC, Kinch MS. Antibody targeting of the EphA2 tyrosine kinase inhibits malignant cell behavior. *Cancer Res.*, 62:2840-2847, 2002). However, EphA2 is expressed ubiquitously in adult tissues, indicating much more possibility of toxicity in treatment of antibody therapy. To investigate the growth or survival effect of EphA4 on PDACa cells, the present inventors knocked down their endogenous expression of EphA4 specifically by siRNA in PDACa cell line. The transfection of the siRNA-producing vectors clearly resulted in reduction of the endogenous expression in one designed siRNA, 1313si, for EphA4 (Figure 7A). This knocking-down effect by the siRNA on EphA4 mRNA resulted in drastic growth suppression in colony formation assay (Figure 7B) and MTT assay (Figure 7C). Considering its tyrosine kinase activity, membrane localization and its specific expression pattern, EphA4 is one the most ideal molecular targets for pancreatic cancer.

In conclusion, the present inventors identified four membrane-type molecules over-expressed in PDACa cells and all of them are likely to be associated with cancer cell growth, suggested these membrane-type molecules are ideal molecular targets for deadly pancreatic cancer treatment and antibodies against these membrane molecules are promising therapeutic approach.

Industrial Applicability

The present inventors have shown that the cell growth is suppressed by small interfering RNA (siRNA) that specifically target the PCDH1, CDH3, GPR107 or EphA4 gene. Thus, this novel siRNAs are useful target for the development of anti-cancer pharmaceuticals. For example, agents that block the expression of PCDH1, CDH3, GPR107 or EphA4 or prevent its activity may find therapeutic utility as anti-cancer agents, particularly anti-cancer agents for the treatment of pancreatic cancer, such as pancreatic ductal adenocarcinoma (PDACa).

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope of the invention.

References

(1) Sharp PA. RNAi and double-strand RNA. Genes Dev. 1999 Jan 15;13(2):139-41..

(2) Hammond SM, Bernstein E, Beach D, Hannon GJ. An RNA-directed nuclease mediates post-transcriptional gene silencing in Drosophila cells. Nature. 2000 Mar 16;404(6775):293-6.

(3) Hannon GJ. RNA interference. Nature. 2002 Jul 11;418(6894):244-51.

(4) Elbashir SM, Harborth J, Lendeckel W, Yalcin A, Weber K, Tuschl T. Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells. Nature. 2001 May 24;411(6836):494-8.

(5) Miyagishi M, Taira K. U6 promoter-driven siRNAs with four uridine 3' overhangs efficiently suppress targeted gene expression in mammalian cells.Nat Biotechnol. 2002 May;20(5):497-500

(6) Brummelkamp TR, Bernards R, Agami R. A System for Stable Expression of Short Interfering RNAs in Mammalian Cells Science. 296(5567):550-553, April 19, 2002.

CLAIMS

1. A method for treating or preventing pancreatic cancer in a subject comprising administering to said subject a composition comprising a small interfering RNA (siRNA) of *PCDH1*, *CDH3*, *GPR107* or *EPHA4*.

2. The method of claim 1, wherein said siRNA comprises a sense nucleic acid and an anti-sense nucleic acid of *PCDH1*, *CDH3*, *GPR107* or *EPHA4*.

3. The method of claim 1, wherein the pancreatic cancer is an pancreatic ductal adenocarcinoma (PDACa).

4. The method of claim 2, wherein the siRNA comprises a ribonucleotide sequence corresponding to a sequence selected from the group consisting of SEQ ID NOs: 54, 57, 60 and 66 as the target sequence.

5. The method of claim 4, said siRNA has the general formula 5'-[A]-[B]-[A']-3', wherein [A] is a ribonucleotide sequence corresponding to a sequence selected from the group consisting of nucleotides of SEQ ID NOs: 54, 57, 60 and 66. [B] is a ribonucleotide sequence consisting of 3 to 23 nucleotides, and [A'] is a ribonucleotide sequence consisting of the complementary sequence of [A].

6. The method of claim 1, wherein said composition comprises a transfection-enhancing agent.

7. A double-stranded molecule comprising a sense strand and an antisense strand, wherein the sense strand comprises a ribonucleotide sequence corresponding to a target sequence selected from the group consisting of SEQ ID NOs: 54, 57, 60 and 66, and wherein the antisense strand comprises a ribonucleotide sequence which is complementary to said sense strand, wherein said sense strand and said antisense strand hybridize to each other to form said double-stranded molecule, and wherein said double-stranded molecule, when introduced into a cell expressing the *PCDH1*, *CDH3*, *GPR107* or *EPHA4* gene, inhibits expression of said gene.

8. The double-stranded molecule of claim 7, wherein said target sequence comprises at least about 10 contiguous nucleotides from the nucleotide sequences selected from the group of SEQ ID NOs: 1, 3, 5, and 7.

9. The double-stranded molecule of claim 8, wherein said target sequence comprises from about 19 to about 25 contiguous nucleotides from the nucleotide sequences selected from the group of SEQ ID NOs: 1, 3, 5, and 7.

10. The double-stranded molecule of claim 9, wherein said double-stranded molecule is a single ribonucleotide transcript comprising the sense strand and the antisense strand linked via a single-stranded ribonucleotide sequence.

11. The double-stranded molecule of claim 8, wherein the double-stranded molecule is an oligonucleotide of less than about 100 nucleotides in length.

12. The double-stranded molecule of claim 11, wherein the double-stranded molecule is an oligonucleotide of less than about 75 nucleotides in length.

13. The double-stranded molecule of claim 12, wherein the double-stranded molecule is an oligonucleotide of less than about 50 nucleotides in length.

14. The double-stranded molecule of claim 13, wherein the double-stranded molecule is an oligonucleotide of less than about 25 nucleotides in length.

15. The double-stranded polynucleotide of claim 14, wherein the double stranded molecule is an oligonucleotide of between about 19 and about 25 nucleotides in length.

16. A vector encoding the double-stranded molecule of claim 8.

17. The vector of claim 16, wherein the vector encodes a transcript having a secondary structure and comprises the sense strand and the antisense strand.

18. The vector of claim 17, wherein the transcript further comprises a single-stranded ribonucleotide sequence linking said sense strand and said antisense strand.

19. A vector comprising a polynucleotide comprising a combination of a sense strand nucleic acid and an antisense strand nucleic acid, wherein said sense strand nucleic acid comprises nucleotide sequence of SEQ ID NOs: 54, 57, 60 and 66, and said antisense strand nucleic acid consists of a sequence complementary to the sense strand.

20. The vector of claim 19, wherein said polynucleotide has the general formula

5'-[A]-[B]-[A']-3'

wherein [A] is a nucleotide sequence of SEQ ID NOs: 54, 57, 60 and 66; [B] is a nucleotide sequence consisting of 3 to 23 nucleotides; and [A'] is a nucleotide sequence complementary to [A].

21. A pharmaceutical composition for treating or preventing pancreatic cancer comprising a pharmaceutically effective amount of a small interfering RNA (siRNA) of *PCDH1*, *CDH3*, *GPR107* or *EPHA4* as an active ingredient, and a pharmaceutically acceptable carrier..

22. The pharmaceutical composition of claim 21, wherein the siRNA comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 54, 57, 60 and 66 as the target sequence.

23. The composition of claim 22, wherein the siRNA has the general formula

5'-[A]-[B]-[A']-3'

wherein [A] is a ribonucleotide sequence corresponding to a nucleotide sequence of SEQ ID NOs: 54, 57, 60 and 66; [B] is a ribonucleotide sequence consisting of 3 to 23 nucleotides; and [A'] is a ribonucleotide sequence complementary to [A].

****

ABSTRACT

The invention features a method for inhibiting growth of a cancer cell by contacting the cell with a composition of a siRNA of *PCDH1*, *CDH3*, *GPR107* or *EPHA4*. Methods of treating cancer are also within the invention. The invention also features products, including nucleic acid sequences and vectors as well as to compositions comprising them, useful in the provided methods. The invention also provides a method for inhibiting of tumor cell, for example pancreatic cancer cell, particularly pancreatic ductal adenocarcinoma (PDACa).

Fig. 1

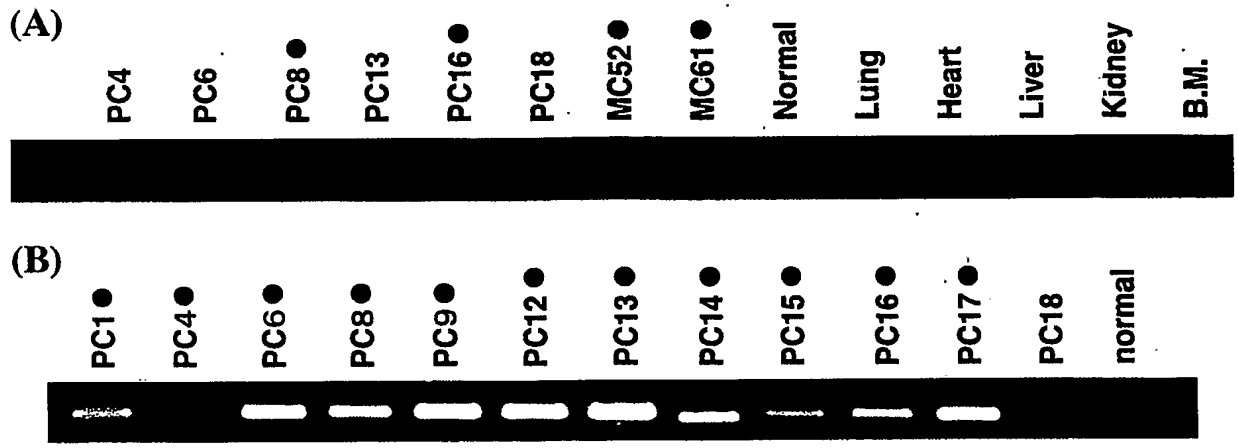
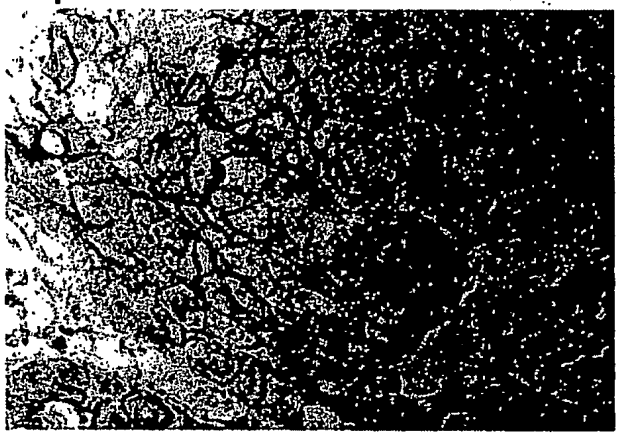


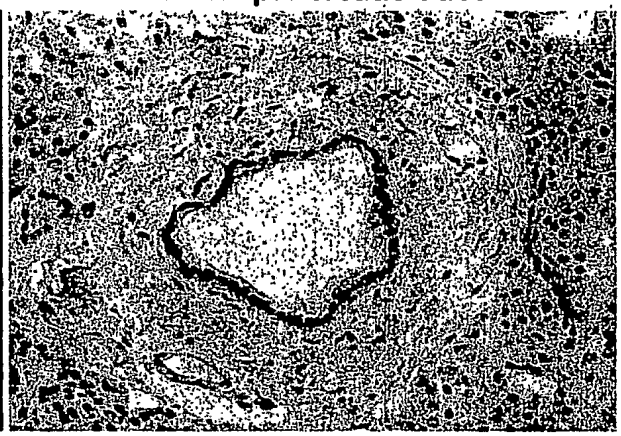
Fig. 2

(A) CDH3

pancreatic ductal adenocarcinoma

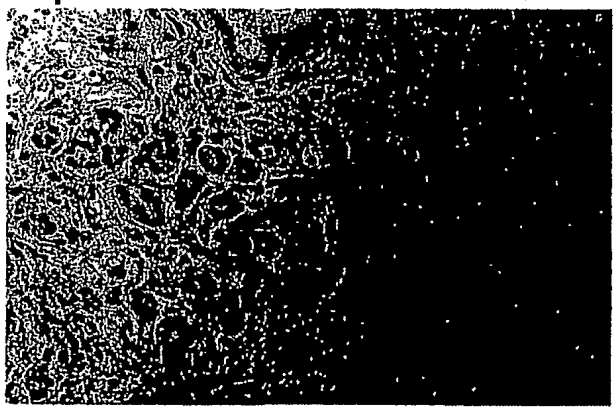


normal pancreatic duct



(B) EphA4

pancreatic ductal adenocarcinoma



normal pancreatic duct

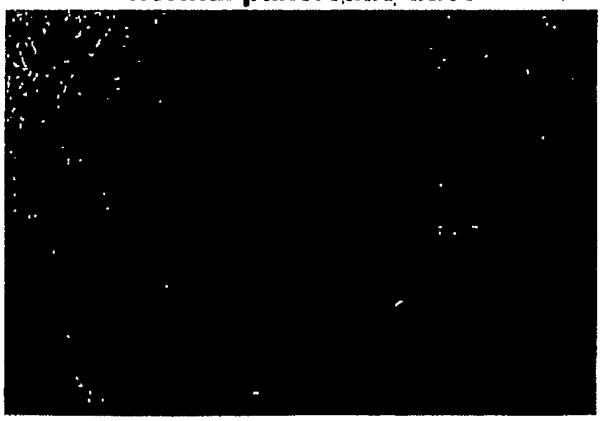
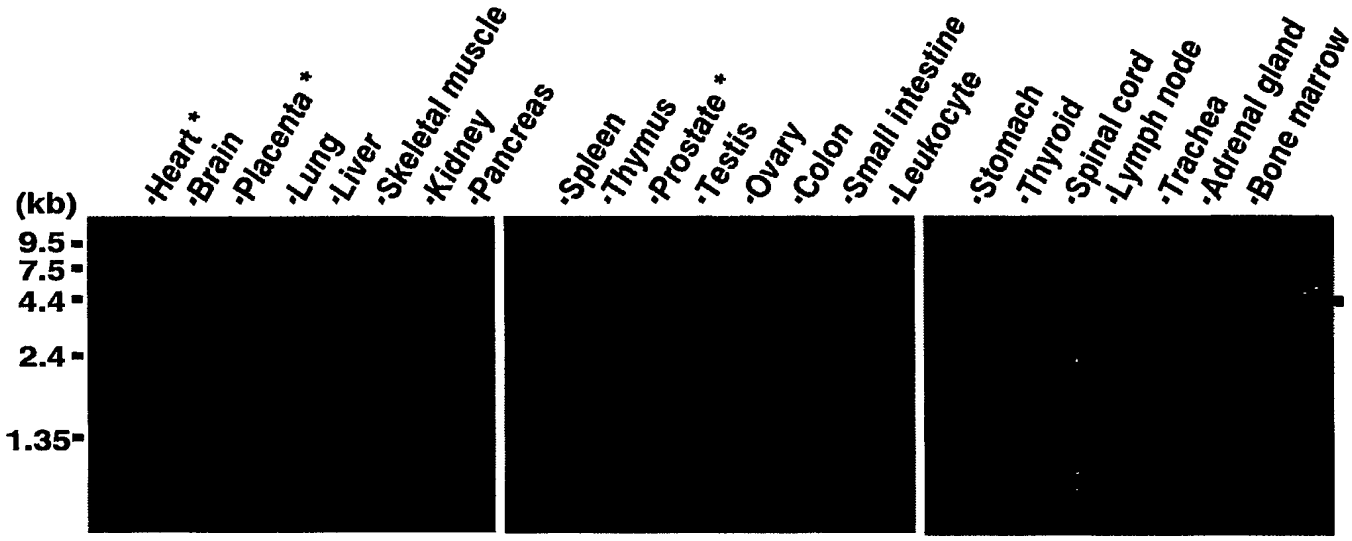


Fig. 3-1

(A) PCDH1



(B)CDH3

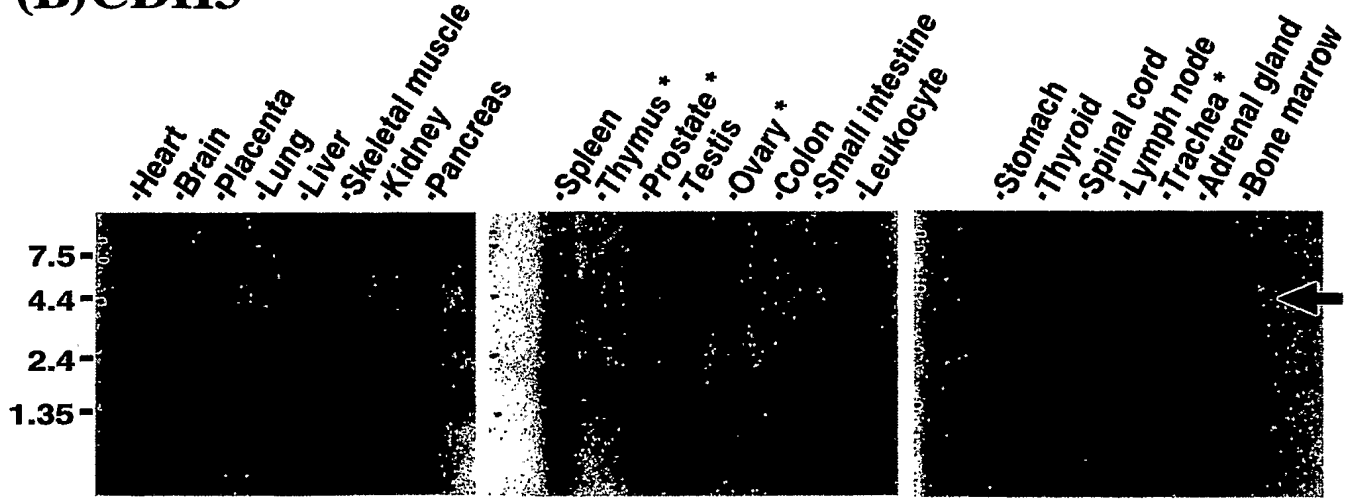


Fig. 3-2

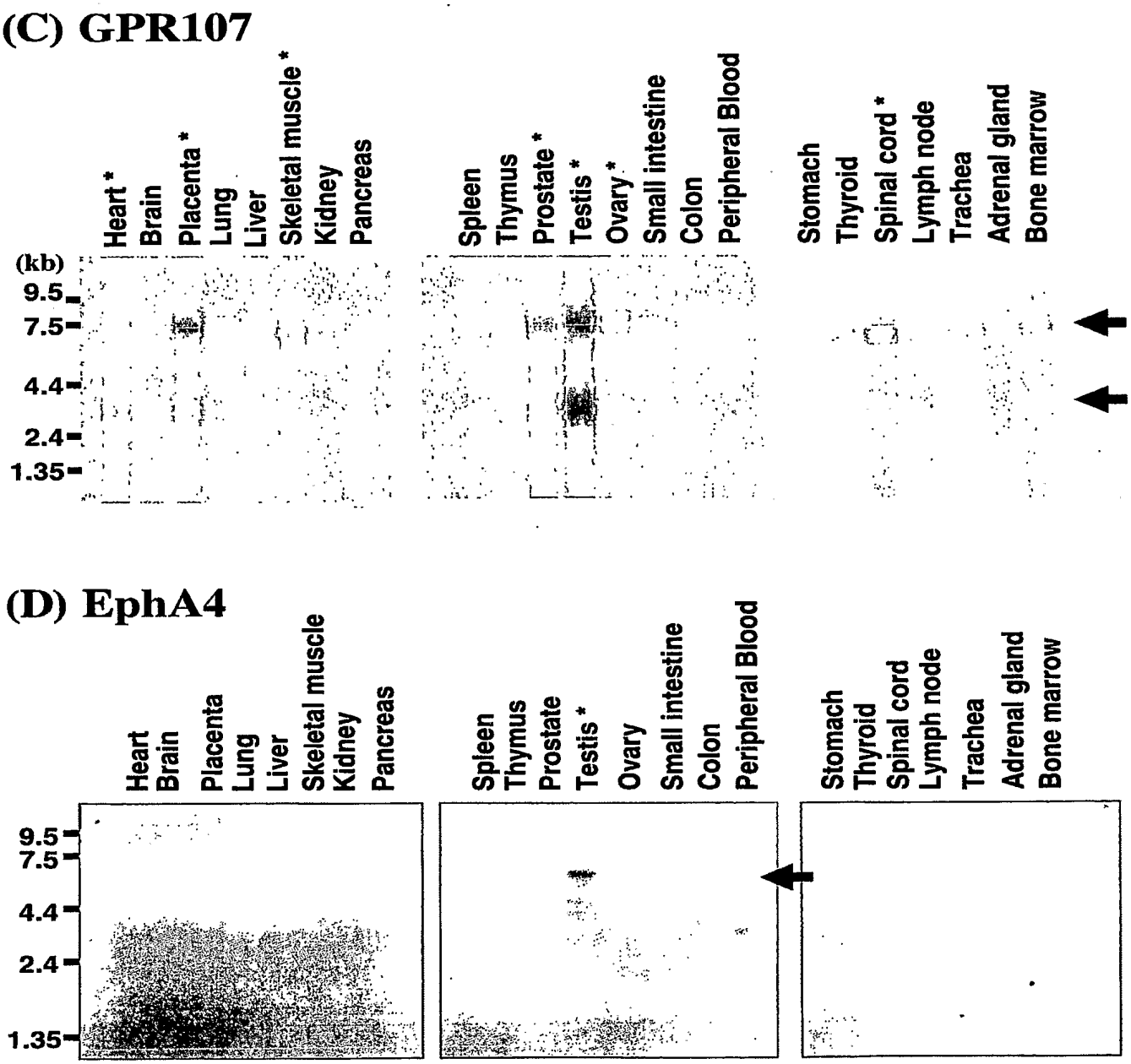


Fig. 4

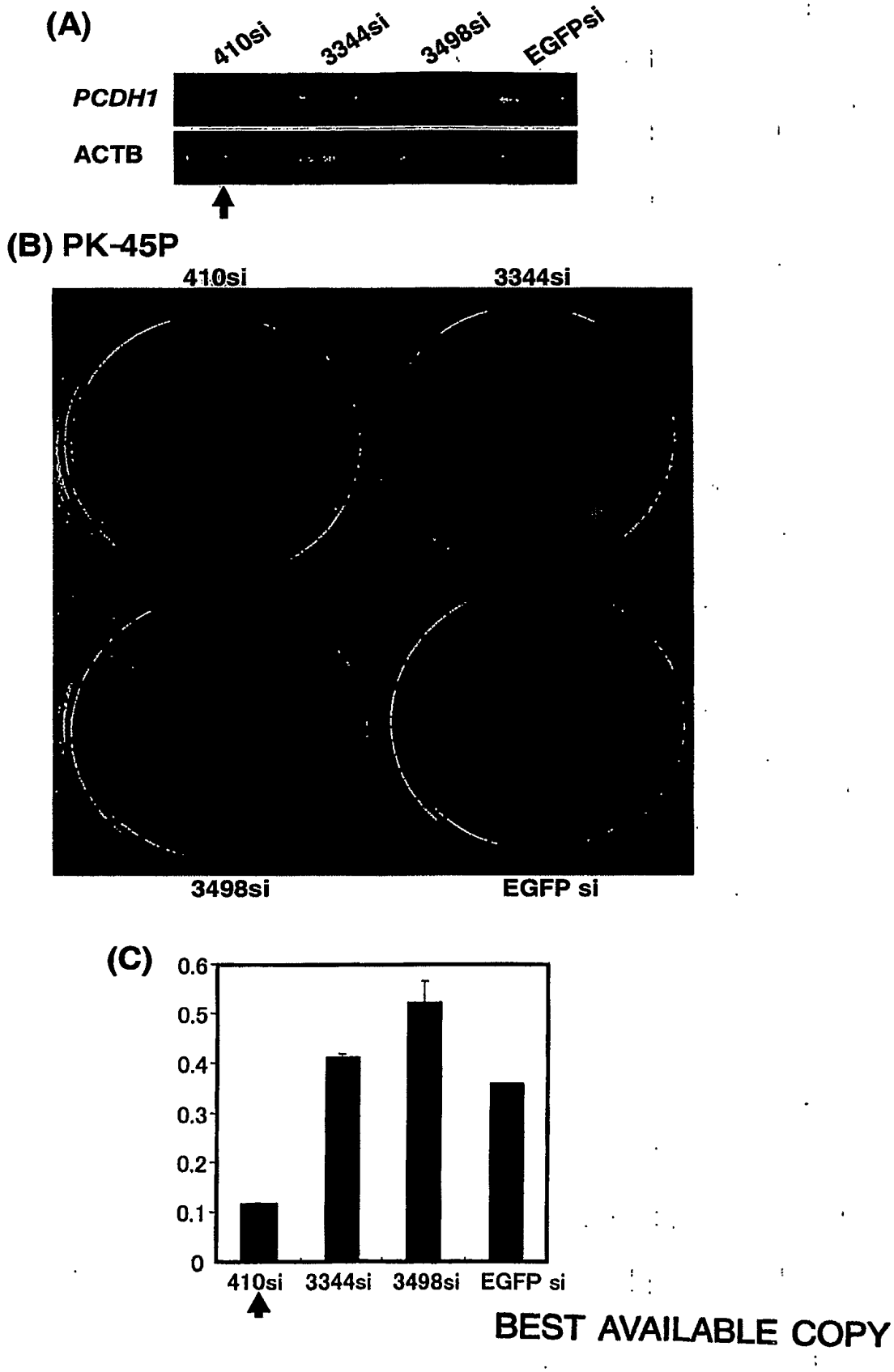


Fig. 5

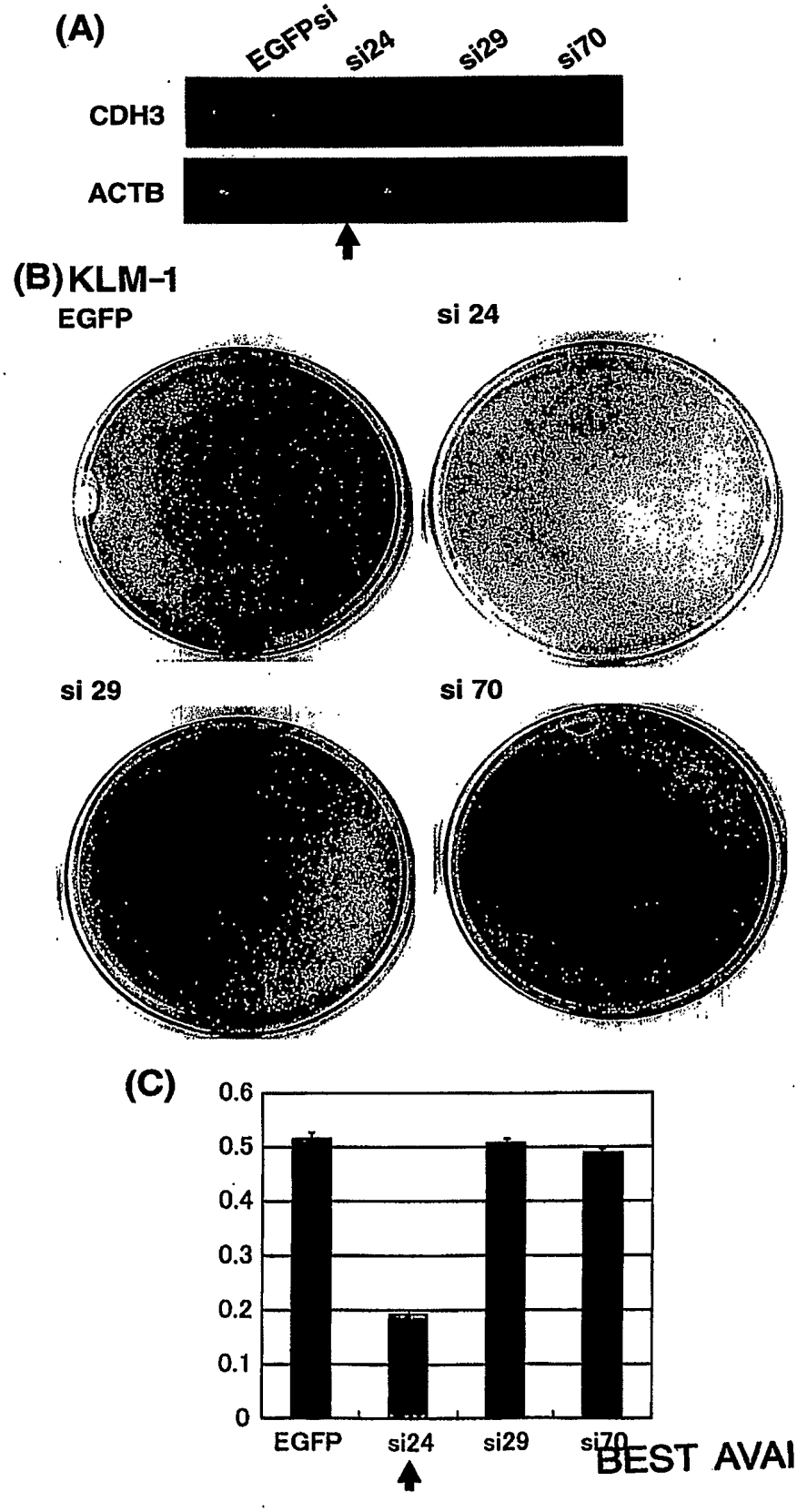


Fig. 6

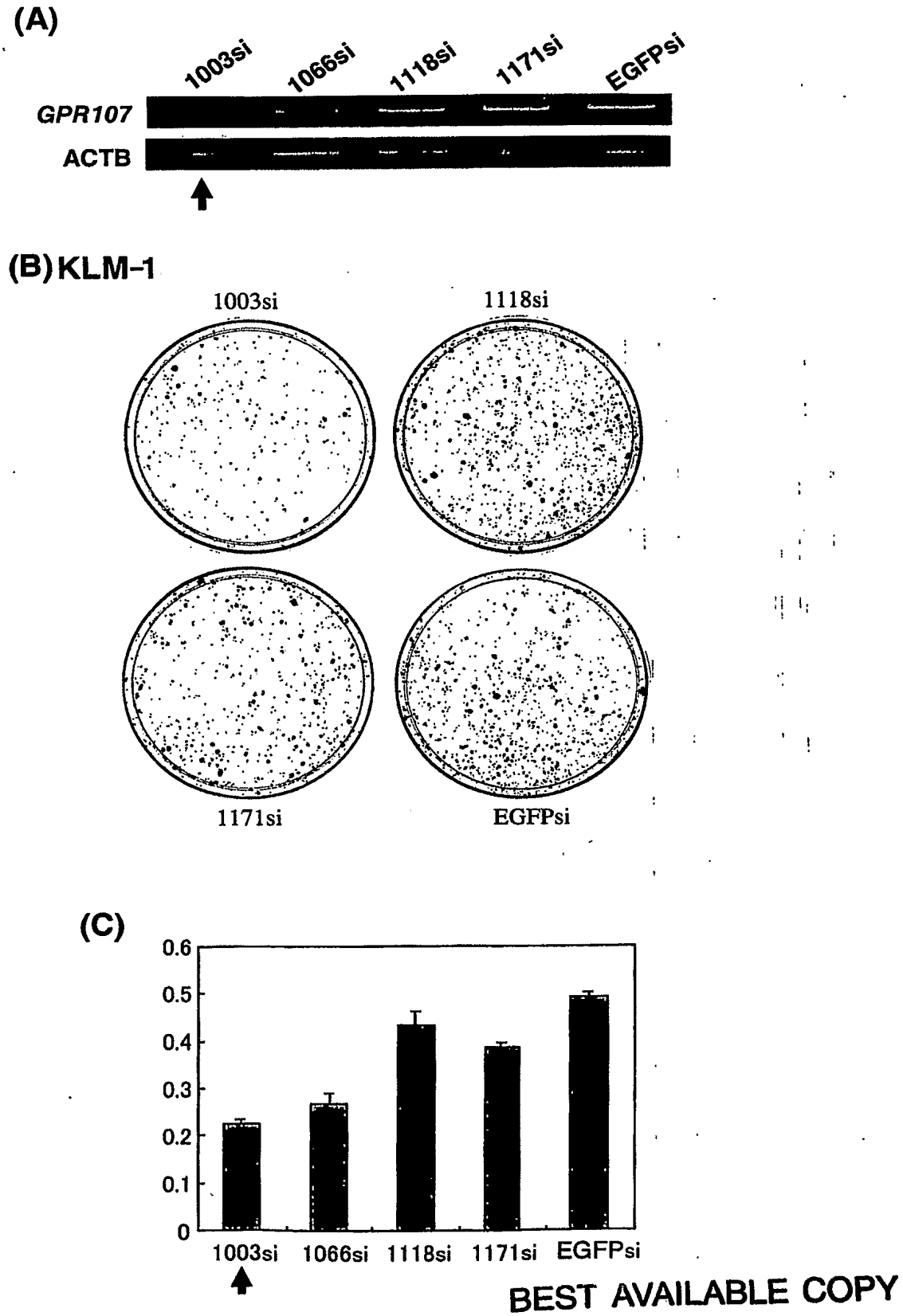
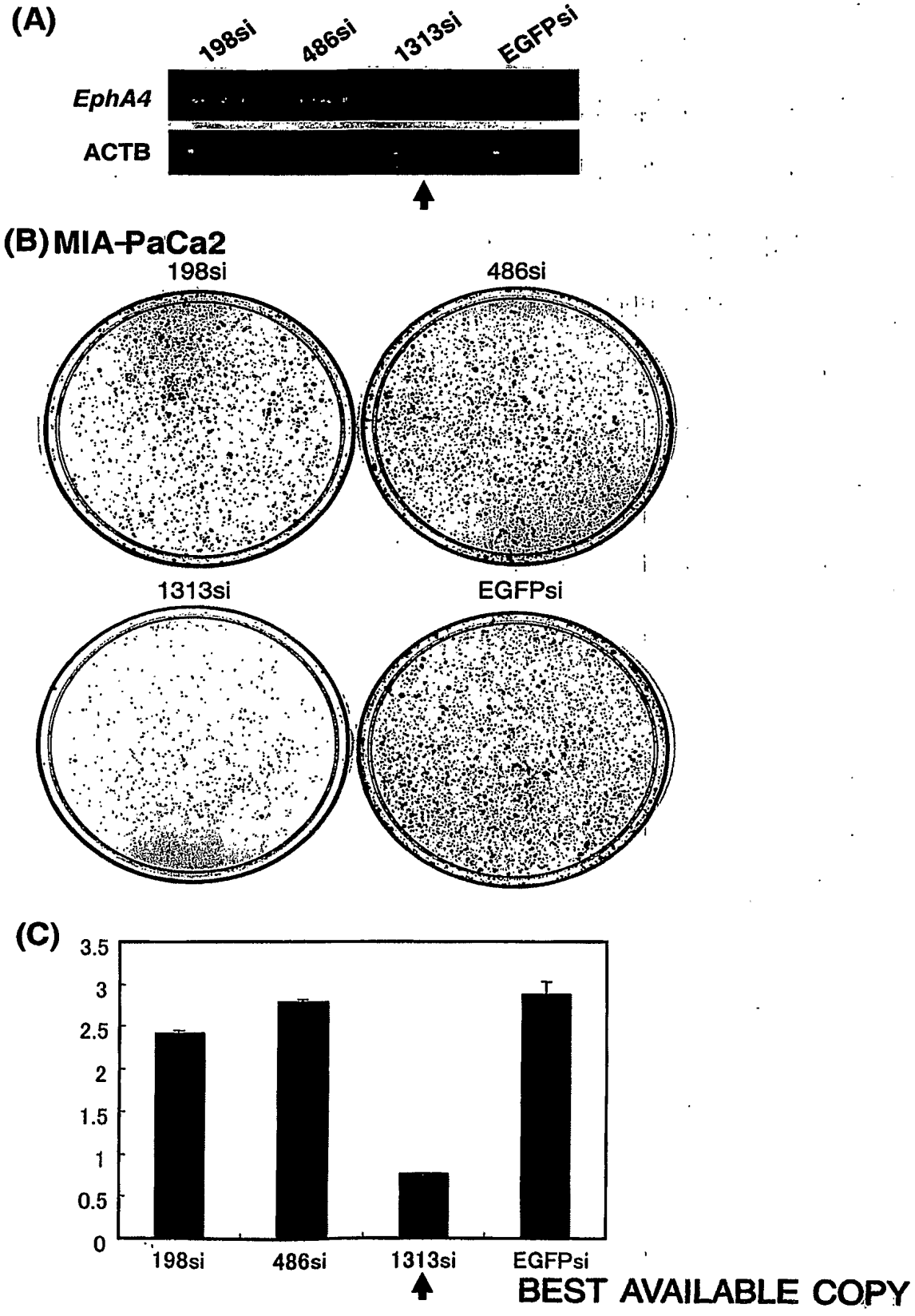


Fig. 8



SEQUENCE LISTING

<110> Nakamura, Yusuke
Nakagawa, Hidewaki

<120> COMPOSITIONS AND METHODS FOR TREATING PANCREATIC CANCER

<130> ONC-PRV0406/US

<160> 75

<170> PatentIn version 3.1

<210> 1
<211> 3851
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (118)..(3300)
<223>

<400> 1
cgcaaagccg ccgggctgct gcgcccagag ccagccggag ccggagccgg agcccgaact 60

gcagctccag ccccagccgt gcggagccgc agcccaggcc ggggccggcg gcggctc 117

atg gac agc ggg gcg ggc ggc cgg cgc tgc ccg gag gcg gcc ctc ctg 165
Met Asp Ser Gly Ala Gly Gly Arg Arg Cys Pro Glu Ala Ala Leu Leu
1 5 10 15

att ctg ggg cct ccc agg atg gag cac ctg agg cac agc cca ggc cct 213
Ile Leu Gly Pro Pro Arg Met Glu His Leu Arg His Ser Pro Gly Pro
20 25 30

ggg ggg caa cgg cta ctg ctg ccc tcc atg ctg cta gca ctg ctg ctc 261
Gly Gly Gln Arg Leu Leu Leu Pro Ser Met Leu Leu Ala Leu Leu Leu
35 40 45

ctg ctg gct cca tcc cca ggc cac gcc act cgg gta gtg tac aag gtg 309
Leu Leu Ala Pro Ser Pro Gly His Ala Thr Arg Val Val Tyr Lys Val
50 55 60

ccg gag gaa cag cca ccc aac acc ctc att ggg agc ctc gca gcc gac 357
Pro Glu Glu Gln Pro Pro Asn Thr Leu Ile Gly Ser Leu Ala Ala Asp
65 70 75 80

tat ggt ttt cca gat gtg ggg cac ctg tac aag cta gag gtg ggt gcc 405
Tyr Gly Phe Pro Asp Val Gly His Leu Tyr Lys Leu Glu Val Gly Ala
85 90 95

ccg tac ctt cgc gtg gat ggc aag aca ggt gac att ttc acc acc gag 453
Pro Tyr Leu Arg Val Asp Gly Lys Thr Gly Asp Ile Phe Thr Thr Glu
100 105 110

acc tcc atc gac cgt gag ggg ctc cgt gaa tgc cag aac cag ctc cct 501
Thr Ser Ile Asp Arg Glu Gly Leu Arg Glu Cys Gln Asn Gln Leu Pro
115 120 125

```
ggt gat ccc tgc atc ctg gag ttt gag gta tct atc aca gac ctc gtg      549
Gly Asp Pro Cys Ile Leu Glu Phe Glu Val Ser Ile Thr Asp Leu Val
    130                 135                 140

cag aat ggc agc ccc cgg ctg cta gag ggc cag ata gaa gta caa gac      597
Gln Asn Gly Ser Pro Arg Leu Leu Glu Gly Gln Ile Glu Val Gln Asp
145                 150                 155                 160

atc aat gac aac aca ccc aac ttc gcc tca cca gtc atc act ctg gcc      645
Ile Asn Asp Asn Thr Pro Asn Phe Ala Ser Pro Val Ile Thr Leu Ala
                165                 170                 175

atc cct gag aac acc aac atc ggc tca ctc ttc ccc atc ccg ctg gct      693
Ile Pro Glu Asn Thr Asn Ile Gly Ser Leu Phe Pro Ile Pro Leu Ala
            180                 185                 190

tca gac cgt gat gct ggt ccc aac ggt gtg gca tcc tat gag ctg cag      741
Ser Asp Arg Asp Ala Gly Pro Asn Gly Val Ala Ser Tyr Glu Leu Gln
        195                 200                 205

gct ggg cct gag gcc cag gag cta ttt ggg ctg cag gtg gca gag gac      789
Ala Gly Pro Glu Ala Gln Glu Leu Phe Gly Leu Gln Val Ala Glu Asp
    210                 215                 220

cag gag gag aag caa cca cag ctc att gtg atg ggc aac ctg gac cgt      837
Gln Glu Glu Lys Gln Pro Gln Leu Ile Val Met Gly Asn Leu Asp Arg
225                 230                 235                 240

gag cgc tgg gac tcc tat gac ctc acc atc aag gtg cag gat ggc ggc      885
Glu Arg Trp Asp Ser Tyr Asp Leu Thr Ile Lys Val Gln Asp Gly Gly
                245                 250                 255

agc ccc cca cgc gcc agc agt gcc ctg ctg cgt gtc acc gtg ctt gac      933
Ser Pro Pro Arg Ala Ser Ser Ala Leu Leu Arg Val Thr Val Leu Asp
            260                 265                 270

acc aat gac aac gcc ccc aag ttt gag cgg ccc tcc tat gag gcc gaa      981
Thr Asn Asp Asn Ala Pro Lys Phe Glu Arg Pro Ser Tyr Glu Ala Glu
        275                 280                 285

cta tct gag aat agc ccc ata ggc cac tcg gtc atc cag gtg aag gcc     1029
Leu Ser Glu Asn Ser Pro Ile Gly His Ser Val Ile Gln Val Lys Ala
    290                 295                 300

aat gac tca gac caa ggt gcc aat gca gaa atc gaa tac aca ttc cac     1077
Asn Asp Ser Asp Gln Gly Ala Asn Ala Glu Ile Glu Tyr Thr Phe His
305                 310                 315                 320

cag gcg ccc gaa gtt gtg agg cgt ctt ctt cga ctg gac agg aac act     1125
Gln Ala Pro Glu Val Val Arg Arg Leu Leu Arg Leu Asp Arg Asn Thr
                325                 330                 335

gga ctt atc act gtt cag ggc ccg gtg gac cgt gag gac cta agc acc     1173
Gly Leu Ile Thr Val Gln Gly Pro Val Asp Arg Glu Asp Leu Ser Thr
            340                 345                 350

ctg cgc ttc tca gtg ctt gct aag gac cga ggc acc aac ccc aag agt     1221
Leu Arg Phe Ser Val Leu Ala Lys Asp Arg Gly Thr Asn Pro Lys Ser
        355                 360                 365
```

```
gcc cgt gcc cag gtg gtt gtg acc gtg aag gac atg aat gac aat gcc      1269
Ala Arg Ala Gln Val Val Val Thr Val Lys Asp Met Asn Asp Asn Ala
    370                 375                 380

ccc acc att gag atc cgg ggc ata ggg cta gtg act cat caa gat ggg      1317
Pro Thr Ile Glu Ile Arg Gly Ile Gly Leu Val Thr His Gln Asp Gly
385                 390                 395                 400

atg gct aac atc tca gag gat gtg gca gag gag aca gct gtg gcc ctg      1365
Met Ala Asn Ile Ser Glu Asp Val Ala Glu Glu Thr Ala Val Ala Leu
                405                 410                 415

gtg cag gtg tct gac cga gat gag gga gag aat gca gct gtc acc tgt      1413
Val Gln Val Ser Asp Arg Asp Glu Gly Glu Asn Ala Ala Val Thr Cys
            420                 425                 430

gtg gtg gca ggt gat gtg ccc ttc cag ctg cgc cag gcc agt gag aca      1461
Val Val Ala Gly Asp Val Pro Phe Gln Leu Arg Gln Ala Ser Glu Thr
        435                 440                 445

ggc agt gac agc aag aag aag tat ttc ctg cag act acc acc ccg cta      1509
Gly Ser Asp Ser Lys Lys Lys Tyr Phe Leu Gln Thr Thr Thr Pro Leu
    450                 455                 460

gac tac gag aag gtc aaa gac tac acc att gag att gtg gct gtg gac      1557
Asp Tyr Glu Lys Val Lys Asp Tyr Thr Ile Glu Ile Val Ala Val Asp
465                 470                 475                 480

tct ggc aac ccc cca ctc tcc agc act aac tcc ctc aag gtg cag gtg      1605
Ser Gly Asn Pro Pro Leu Ser Ser Thr Asn Ser Leu Lys Val Gln Val
                485                 490                 495

gtg gac gtc aat gac aac gca cct gtc ttc act cag agt gtc act gag      1653
Val Asp Val Asn Asp Asn Ala Pro Val Phe Thr Gln Ser Val Thr Glu
            500                 505                 510

gtc gcc ttc ccg gaa aac aac aag cct ggt gaa gtg att gct gag atc      1701
Val Ala Phe Pro Glu Asn Asn Lys Pro Gly Glu Val Ile Ala Glu Ile
        515                 520                 525

act gcc agt gat gct gac tct ggc tct aat gct gag ctg gtt tac tct      1749
Thr Ala Ser Asp Ala Asp Ser Gly Ser Asn Ala Glu Leu Val Tyr Ser
    530                 535                 540

ctg gag cct gag ccg gct gct aag ggc ctc ttc acc atc tca ccc gag      1797
Leu Glu Pro Glu Pro Ala Ala Lys Gly Leu Phe Thr Ile Ser Pro Glu
545                 550                 555                 560

act gga gag atc cag gtg aag aca tct ctg gat cgg gaa cag cgg gag      1845
Thr Gly Glu Ile Gln Val Lys Thr Ser Leu Asp Arg Glu Gln Arg Glu
                565                 570                 575

agc tat gag ttg aag gtg gtg gca gct gac cgg ggc agt cct agc ctc      1893
Ser Tyr Glu Leu Lys Val Val Ala Ala Asp Arg Gly Ser Pro Ser Leu
            580                 585                 590

cag ggc aca gcc act gtc ctt gtc aat gtg ctg gac tgc aat gac aat      1941
Gln Gly Thr Ala Thr Val Leu Val Asn Val Leu Asp Cys Asn Asp Asn
        595                 600                 605
```

```
gac ccc aaa ttt atg ctg agt ggc tac aac ttc tca gtg atg gag aac      1989
Asp Pro Lys Phe Met Leu Ser Gly Tyr Asn Phe Ser Val Met Glu Asn
    610                 615                 620

atg cca gca ctg agt cca gtg ggc atg gtg act gtc att gat gga gac      2037
Met Pro Ala Leu Ser Pro Val Gly Met Val Thr Val Ile Asp Gly Asp
625                 630                 635                 640

aag ggg gag aat gcc cag gtg cag ctc tca gtg gag cag gac aac ggt      2085
Lys Gly Glu Asn Ala Gln Val Gln Leu Ser Val Glu Gln Asp Asn Gly
                645                 650                 655

gac ttt gtt atc cag aat ggc aca ggc acc atc cta tcc agc ctg agc      2133
Asp Phe Val Ile Gln Asn Gly Thr Gly Thr Ile Leu Ser Ser Leu Ser
            660                 665                 670

ttt gat cga gag caa caa agc acc tac acc ttc cag ctg aag gca gtg      2181
Phe Asp Arg Glu Gln Gln Ser Thr Tyr Thr Phe Gln Leu Lys Ala Val
        675                 680                 685

gat ggt ggc gtc cca cct cgc tca gct tac gtt ggt gtc acc atc aat      2229
Asp Gly Gly Val Pro Pro Arg Ser Ala Tyr Val Gly Val Thr Ile Asn
    690                 695                 700

gtg ctg gac gag aat gac aac gca ccc tat atc act gcc cct tct aac      2277
Val Leu Asp Glu Asn Asp Asn Ala Pro Tyr Ile Thr Ala Pro Ser Asn
705                 710                 715                 720

acc tct cac aag ctg ctg acc ccc cag aca cgt ctt ggt gag acg gtc      2325
Thr Ser His Lys Leu Leu Thr Pro Gln Thr Arg Leu Gly Glu Thr Val
                725                 730                 735

agc cag gtg gca gcc gag gac ttt gac tct ggt gtc aat gct gag ctg      2373
Ser Gln Val Ala Ala Glu Asp Phe Asp Ser Gly Val Asn Ala Glu Leu
            740                 745                 750

atc tac agc att gca ggt ggc aac cct tat gga ctc ttc cag att ggg      2421
Ile Tyr Ser Ile Ala Gly Gly Asn Pro Tyr Gly Leu Phe Gln Ile Gly
        755                 760                 765

tca cat tca ggt gcc atc acc ctg gag aag gag att gag cgg cgc cac      2469
Ser His Ser Gly Ala Ile Thr Leu Glu Lys Glu Ile Glu Arg Arg His
    770                 775                 780

cat ggg cta cac cgc ctg gtg gtg aag gtc agt gac cgc ggc aag ccc      2517
His Gly Leu His Arg Leu Val Val Lys Val Ser Asp Arg Gly Lys Pro
785                 790                 795                 800

cca cgc tat ggc aca gcc ttg gtc cat ctt tat gtc aat gag act ctg      2565
Pro Arg Tyr Gly Thr Ala Leu Val His Leu Tyr Val Asn Glu Thr Leu
                805                 810                 815

gcc aac cgc acg ctg ctg gag acc ctc ctg ggc cac agc ctg gac acg      2613
Ala Asn Arg Thr Leu Leu Glu Thr Leu Leu Gly His Ser Leu Asp Thr
            820                 825                 830

ccg ctg gat att gac att gct ggg gat cca gaa tat gag cgc tcc aag      2661
Pro Leu Asp Ile Asp Ile Ala Gly Asp Pro Glu Tyr Glu Arg Ser Lys
        835                 840                 845
```

```
cag cgt ggc aac att ctc ttt ggt gtg gtg gct ggt gtg gtg gcc gtg      2709
Gln Arg Gly Asn Ile Leu Phe Gly Val Val Ala Gly Val Val Ala Val
    850                 855                 860

gcc ttg ctc atc gcc ctg gcg gtt ctt gtg cgc tac tgc aga cag cgg      2757
Ala Leu Leu Ile Ala Leu Ala Val Leu Val Arg Tyr Cys Arg Gln Arg
865                 870                 875                 880

gag gcc aaa agt ggt tac cag gct ggt aag aag gag acc aag gac ctg      2805
Glu Ala Lys Ser Gly Tyr Gln Ala Gly Lys Lys Glu Thr Lys Asp Leu
                885                 890                 895

tat gcc ccc aag ccc agt ggc aag gcc tcc aag gga aac aaa agc aaa      2853
Tyr Ala Pro Lys Pro Ser Gly Lys Ala Ser Lys Gly Asn Lys Ser Lys
            900                 905                 910

ggc aag aag agc aag tcc cca aag ccc gtg aag cca gtg gag gac gag      2901
Gly Lys Lys Ser Lys Ser Pro Lys Pro Val Lys Pro Val Glu Asp Glu
        915                 920                 925

gat gag gcc ggg ctg cag aag tcc ctc aag ttc aac ctg atg agc gat      2949
Asp Glu Ala Gly Leu Gln Lys Ser Leu Lys Phe Asn Leu Met Ser Asp
    930                 935                 940

gcc cct ggg gac agt ccc cgc atc cac ctg ccc ctc aac tac cca cca      2997
Ala Pro Gly Asp Ser Pro Arg Ile His Leu Pro Leu Asn Tyr Pro Pro
945                 950                 955                 960

ggc agc cct gac ctg ggc cgc cac tat cgc tct aac tcc cca ctg cct      3045
Gly Ser Pro Asp Leu Gly Arg His Tyr Arg Ser Asn Ser Pro Leu Pro
                965                 970                 975

tcc atc cag ctg cag ccc cag tca ccc tca gcc tcc aag aag cac cag      3093
Ser Ile Gln Leu Gln Pro Gln Ser Pro Ser Ala Ser Lys Lys His Gln
            980                 985                 990

gtg gta cag gac ctg cca cct gca  aac aca ttc gtg ggc  acc ggg gac    3141
Val Val Gln Asp Leu Pro Pro Ala  Asn Thr Phe Val Gly  Thr Gly Asp
        995                 1000                1005

acc acg  tcc acg ggc tct gag  cag tac tcc gac tac  agc tac cgc       3186
Thr Thr  Ser Thr Gly Ser Glu  Gln Tyr Ser Asp Tyr  Ser Tyr Arg
    1010                1015                1020

acc aac  ccc ccc aaa tac ccc  agc aag cag gta ggc  cag ccc ttt       3231
Thr Asn  Pro Pro Lys Tyr Pro  Ser Lys Gln Val Gly  Gln Pro Phe
    1025                1030                1035

cag ctc  agc aca ccc cag ccc  cta ccc cac ccc tac  cac gga gcc       3276
Gln Leu  Ser Thr Pro Gln Pro  Leu Pro His Pro Tyr  His Gly Ala
    1040                1045                1050

atc tgg  acc gag gtg tgg gag  tga tggagcaggt ttactgtgcc             3320
Ile Trp  Thr Glu Val Trp Glu
    1055                1060

tgcccgtgtt gggggccagc ctgagccagc agtgggaggt ggggccttag tgcctcaccg   3380
ggcacacgga ttaggctgag tgaagattaa gggagggtgt gctctgtggt ctcctccctg   3440
ccctctcccc actggggaga gacctgtgat ttgccaagtc cctggaccct ggaccagcta   3500
ctgggcctta tgggttgggg gtggtaggca ggtgagcgta agtggggagg gaaatgggta   3560
```

```
agaagtctac tccaaacctа ggtctctatg tcagaccaga cctaggtgct tctctaggag   3620
ggaaacaggg agacctgggg tcctgtggat aactgagtgg ggagtctgcc aggggagggc   3680
accttcccat tgtgccttct gtgtgtattg tgcattaacc tcttcctcac cactaggctt   3740
ctggggctgg gtcccacatg cccttgaccc tgacaataaa gttctctatt tttggaaaaa   3800
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a                      3851
```

<210> 2
<211> 1060
<212> PRT
<213> Homo sapiens

<400> 2

```
Met Asp Ser Gly Ala Gly Gly Arg Arg Cys Pro Glu Ala Ala Leu Leu
1               5                  10                  15

Ile Leu Gly Pro Pro Arg Met Glu His Leu Arg His Ser Pro Gly Pro
            20                  25                  30

Gly Gly Gln Arg Leu Leu Leu Pro Ser Met Leu Leu Ala Leu Leu Leu
        35                  40                  45

Leu Leu Ala Pro Ser Pro Gly His Ala Thr Arg Val Val Tyr Lys Val
    50                  55                  60

Pro Glu Glu Gln Pro Pro Asn Thr Leu Ile Gly Ser Leu Ala Ala Asp
65                  70                  75                  80

Tyr Gly Phe Pro Asp Val Gly His Leu Tyr Lys Leu Glu Val Gly Ala
                85                  90                  95

Pro Tyr Leu Arg Val Asp Gly Lys Thr Gly Asp Ile Phe Thr Thr Glu
            100                 105                 110

Thr Ser Ile Asp Arg Glu Gly Leu Arg Glu Cys Gln Asn Gln Leu Pro
        115                 120                 125

Gly Asp Pro Cys Ile Leu Glu Phe Glu Val Ser Ile Thr Asp Leu Val
    130                 135                 140

Gln Asn Gly Ser Pro Arg Leu Leu Glu Gly Gln Ile Glu Val Gln Asp
145                 150                 155                 160

Ile Asn Asp Asn Thr Pro Asn Phe Ala Ser Pro Val Ile Thr Leu Ala
                165                 170                 175

Ile Pro Glu Asn Thr Asn Ile Gly Ser Leu Phe Pro Ile Pro Leu Ala
            180                 185                 190

Ser Asp Arg Asp Ala Gly Pro Asn Gly Val Ala Ser Tyr Glu Leu Gln
        195                 200                 205

Ala Gly Pro Glu Ala Gln Glu Leu Phe Gly Leu Gln Val Ala Glu Asp
    210                 215                 220

Gln Glu Glu Lys Gln Pro Gln Leu Ile Val Met Gly Asn Leu Asp Arg
225                 230                 235                 240

Glu Arg Trp Asp Ser Tyr Asp Leu Thr Ile Lys Val Gln Asp Gly Gly
                245                 250                 255
```

Ser Pro Pro Arg Ala Ser Ser Ala Leu Leu Arg Val Thr Val Leu Asp
260 265 270

Thr Asn Asp Asn Ala Pro Lys Phe Glu Arg Pro Ser Tyr Glu Ala Glu
275 280 285

Leu Ser Glu Asn Ser Pro Ile Gly His Ser Val Ile Gln Val Lys Ala
290 295 300

Asn Asp Ser Asp Gln Gly Ala Asn Ala Glu Ile Glu Tyr Thr Phe His
305 310 315 320

Gln Ala Pro Glu Val Val Arg Arg Leu Leu Arg Leu Asp Arg Asn Thr
325 330 335

Gly Leu Ile Thr Val Gln Gly Pro Val Asp Arg Glu Asp Leu Ser Thr
340 345 350

Leu Arg Phe Ser Val Leu Ala Lys Asp Arg Gly Thr Asn Pro Lys Ser
355 360 365

Ala Arg Ala Gln Val Val Val Thr Val Lys Asp Met Asn Asp Asn Ala
370 375 380

Pro Thr Ile Glu Ile Arg Gly Ile Gly Leu Val Thr His Gln Asp Gly
385 390 395 400

Met Ala Asn Ile Ser Glu Asp Val Ala Glu Glu Thr Ala Val Ala Leu
405 410 415

Val Gln Val Ser Asp Arg Asp Glu Gly Glu Asn Ala Ala Val Thr Cys
420 425 430

Val Val Ala Gly Asp Val Pro Phe Gln Leu Arg Gln Ala Ser Glu Thr
435 440 445

Gly Ser Asp Ser Lys Lys Lys Tyr Phe Leu Gln Thr Thr Thr Pro Leu
450 455 460

Asp Tyr Glu Lys Val Lys Asp Tyr Thr Ile Glu Ile Val Ala Val Asp
465 470 475 480

Ser Gly Asn Pro Pro Leu Ser Ser Thr Asn Ser Leu Lys Val Gln Val
485 490 495

Val Asp Val Asn Asp Asn Ala Pro Val Phe Thr Gln Ser Val Thr Glu
500 505 510

Val Ala Phe Pro Glu Asn Asn Lys Pro Gly Glu Val Ile Ala Glu Ile
515 520 525

Thr Ala Ser Asp Ala Asp Ser Gly Ser Asn Ala Glu Leu Val Tyr Ser
530 535 540

Leu Glu Pro Glu Pro Ala Ala Lys Gly Leu Phe Thr Ile Ser Pro Glu
545 550 555 560

Thr Gly Glu Ile Gln Val Lys Thr Ser Leu Asp Arg Glu Gln Arg Glu
565 570 575

Ser Tyr Glu Leu Lys Val Val Ala Ala Asp Arg Gly Ser Pro Ser Leu
580 585 590

Gln Gly Thr Ala Thr Val Leu Val Asn Val Leu Asp Cys Asn Asp Asn
595 600 605

Asp Pro Lys Phe Met Leu Ser Gly Tyr Asn Phe Ser Val Met Glu Asn
610 615 620

Met Pro Ala Leu Ser Pro Val Gly Met Val Thr Val Ile Asp Gly Asp
625 630 635 640

Lys Gly Glu Asn Ala Gln Val Gln Leu Ser Val Glu Gln Asp Asn Gly
645 650 655

Asp Phe Val Ile Gln Asn Gly Thr Gly Thr Ile Leu Ser Ser Leu Ser
660 665 670

Phe Asp Arg Glu Gln Gln Ser Thr Tyr Thr Phe Gln Leu Lys Ala Val
675 680 685

Asp Gly Gly Val Pro Pro Arg Ser Ala Tyr Val Gly Val Thr Ile Asn
690 695 700

Val Leu Asp Glu Asn Asp Asn Ala Pro Tyr Ile Thr Ala Pro Ser Asn
705 710 715 720

Thr Ser His Lys Leu Leu Thr Pro Gln Thr Arg Leu Gly Glu Thr Val
725 730 735

Ser Gln Val Ala Ala Glu Asp Phe Asp Ser Gly Val Asn Ala Glu Leu
740 745 750

Ile Tyr Ser Ile Ala Gly Gly Asn Pro Tyr Gly Leu Phe Gln Ile Gly
755 760 765

Ser His Ser Gly Ala Ile Thr Leu Glu Lys Glu Ile Glu Arg Arg His
770 775 780

His Gly Leu His Arg Leu Val Val Lys Val Ser Asp Arg Gly Lys Pro
785 790 795 800

Pro Arg Tyr Gly Thr Ala Leu Val His Leu Tyr Val Asn Glu Thr Leu
805 810 815

Ala Asn Arg Thr Leu Leu Glu Thr Leu Leu Gly His Ser Leu Asp Thr
820 825 830

Pro Leu Asp Ile Asp Ile Ala Gly Asp Pro Glu Tyr Glu Arg Ser Lys
835 840 845

Gln Arg Gly Asn Ile Leu Phe Gly Val Val Ala Gly Val Val Ala Val
850 855 860

Ala Leu Leu Ile Ala Leu Ala Val Leu Val Arg Tyr Cys Arg Gln Arg
865 870 875 880

Glu Ala Lys Ser Gly Tyr Gln Ala Gly Lys Lys Glu Thr Lys Asp Leu
885 890 895

Tyr Ala Pro Lys Pro Ser Gly Lys Ala Ser Lys Gly Asn Lys Ser Lys
900 905 910

Gly Lys Lys Ser Lys Ser Pro Lys Pro Val Lys Pro Val Glu Asp Glu
915 920 925

Asp Glu Ala Gly Leu Gln Lys Ser Leu Lys Phe Asn Leu Met Ser Asp
930 935 940

Ala Pro Gly Asp Ser Pro Arg Ile His Leu Pro Leu Asn Tyr Pro Pro
945 950 955 960

Gly Ser Pro Asp Leu Gly Arg His Tyr Arg Ser Asn Ser Pro Leu Pro
965 970 975

Ser Ile Gln Leu Gln Pro Gln Ser Pro Ser Ala Ser Lys Lys His Gln
980 985 990

Val Val Gln Asp Leu Pro Pro Ala Asn Thr Phe Val Gly Thr Gly Asp
995 1000 1005

Thr Thr Ser Thr Gly Ser Glu Gln Tyr Ser Asp Tyr Ser Tyr Arg
1010 1015 1020

Thr Asn Pro Pro Lys Tyr Pro Ser Lys Gln Val Gly Gln Pro Phe
1025 1030 1035

Gln Leu Ser Thr Pro Gln Pro Leu Pro His Pro Tyr His Gly Ala
1040 1045 1050

Ile Trp Thr Glu Val Trp Glu
1055 1060

<210> 3
<211> 3205
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (71)..(2560)
<223>

<400> 3
aaaggggcaa gagctgagcg gaacaccggc ccgccgtcgc ggcagctgct tcacccctct 60

ctctgcagcc atg ggg ctc cct cgt gga cct ctc gcg tct ctc ctc ctt 109
Met Gly Leu Pro Arg Gly Pro Leu Ala Ser Leu Leu Leu
1 5 10

ctc cag gtt tgc tgg ctg cag tgc gcg gcc tcc gag ccg tgc cgg gcg 157
Leu Gln Val Cys Trp Leu Gln Cys Ala Ala Ser Glu Pro Cys Arg Ala
15 20 25

gtc ttc agg gag gct gaa gtg acc ttg gag gcg gga ggc gcg gag cag 205
Val Phe Arg Glu Ala Glu Val Thr Leu Glu Ala Gly Gly Ala Glu Gln
30 35 40 45

```
gag ccc ggc cag gcg ctg ggg aaa gta ttc atg ggc tgc cct ggg caa      253
Glu Pro Gly Gln Ala Leu Gly Lys Val Phe Met Gly Cys Pro Gly Gln
                50                  55                  60

gag cca gct ctg ttt agc act gat aat gat gac ttc act gtg cgg aat      301
Glu Pro Ala Leu Phe Ser Thr Asp Asn Asp Asp Phe Thr Val Arg Asn
            65                  70                  75

ggc gag aca gtc cag gaa aga agg tca ctg aag gaa agg aat cca ttg      349
Gly Glu Thr Val Gln Glu Arg Arg Ser Leu Lys Glu Arg Asn Pro Leu
        80                  85                  90

aag atc ttc cca tcc aaa cgt atc tta cga aga cac aag aga gat tgg      397
Lys Ile Phe Pro Ser Lys Arg Ile Leu Arg Arg His Lys Arg Asp Trp
    95                  100                 105

gtg gtt gct cca ata tct gtc cct gaa aat ggc aag ggt ccc ttc ccc      445
Val Val Ala Pro Ile Ser Val Pro Glu Asn Gly Lys Gly Pro Phe Pro
110                 115                 120                 125

cag aga ctg aat cag ctc aag tct aat aaa gat aga gac acc aag att      493
Gln Arg Leu Asn Gln Leu Lys Ser Asn Lys Asp Arg Asp Thr Lys Ile
                130                 135                 140

ttc tac agc atc acg ggg ccg ggg gca gac agc ccc cct gag ggt gtc      541
Phe Tyr Ser Ile Thr Gly Pro Gly Ala Asp Ser Pro Pro Glu Gly Val
            145                 150                 155

ttc gct gta gag aag gag aca ggc tgg ttg ttg ttg aat aag cca ctg      589
Phe Ala Val Glu Lys Glu Thr Gly Trp Leu Leu Leu Asn Lys Pro Leu
        160                 165                 170

gac cgg gag gag att gcc aag tat gag ctc ttt ggc cac gct gtg tca      637
Asp Arg Glu Glu Ile Ala Lys Tyr Glu Leu Phe Gly His Ala Val Ser
    175                 180                 185

gag aat ggt gcc tca gtg gag gac ccc atg aac atc tcc atc atc gtg      685
Glu Asn Gly Ala Ser Val Glu Asp Pro Met Asn Ile Ser Ile Ile Val
190                 195                 200                 205

acc gac cag aat gac cac aag ccc aag ttt acc cag gac acc ttc cga      733
Thr Asp Gln Asn Asp His Lys Pro Lys Phe Thr Gln Asp Thr Phe Arg
                210                 215                 220

ggg agt gtc tta gag gga gtc cta cca ggt act tct gtg atg cag gtg      781
Gly Ser Val Leu Glu Gly Val Leu Pro Gly Thr Ser Val Met Gln Val
            225                 230                 235

aca gcc acg gat gag gat gat gcc atc tac acc tac aat ggg gtg gtt      829
Thr Ala Thr Asp Glu Asp Asp Ala Ile Tyr Thr Tyr Asn Gly Val Val
        240                 245                 250

gct tac tcc atc cat agc caa gaa cca aag gac cca cac gac ctc atg      877
Ala Tyr Ser Ile His Ser Gln Glu Pro Lys Asp Pro His Asp Leu Met
    255                 260                 265

ttc acc att cac cgg agc aca ggc acc atc agc gtc atc tcc agt ggc      925
Phe Thr Ile His Arg Ser Thr Gly Thr Ile Ser Val Ile Ser Ser Gly
270                 275                 280                 285
```

```
ctg gac cgg gaa aaa gtc cct gag tac aca ctg acc atc cag gcc aca      973
Leu Asp Arg Glu Lys Val Pro Glu Tyr Thr Leu Thr Ile Gln Ala Thr
                290                 295                 300

gac atg gat ggg gac ggc tcc acc acc acg gca gtg gca gta gtg gag     1021
Asp Met Asp Gly Asp Gly Ser Thr Thr Thr Ala Val Ala Val Val Glu
            305                 310                 315

atc ctt gat gcc aat gac aat gct ccc atg ttt gac ccc cag aag tac     1069
Ile Leu Asp Ala Asn Asp Asn Ala Pro Met Phe Asp Pro Gln Lys Tyr
        320                 325                 330

gag gcc cat gtg cct gag aat gca gtg ggc cat gag gtg cag agg ctg     1117
Glu Ala His Val Pro Glu Asn Ala Val Gly His Glu Val Gln Arg Leu
    335                 340                 345

acg gtc act gat ctg gac gcc ccc aac tca cca gcg tgg cgt gcc acc     1165
Thr Val Thr Asp Leu Asp Ala Pro Asn Ser Pro Ala Trp Arg Ala Thr
350                 355                 360                 365

tac ctt atc atg ggc ggt gac gac ggg gac cat ttt acc atc acc acc     1213
Tyr Leu Ile Met Gly Gly Asp Asp Gly Asp His Phe Thr Ile Thr Thr
                370                 375                 380

cac cct gag agc aac cag ggc atc ctg aca acc agg aag ggt ttg gat     1261
His Pro Glu Ser Asn Gln Gly Ile Leu Thr Thr Arg Lys Gly Leu Asp
            385                 390                 395

ttt gag gcc aaa aac cag cac acc ctg tac gtt gaa gtg acc aac gag     1309
Phe Glu Ala Lys Asn Gln His Thr Leu Tyr Val Glu Val Thr Asn Glu
        400                 405                 410

gcc cct ttt gtg ctg aag ctc cca acc tcc aca gcc acc ata gtg gtc     1357
Ala Pro Phe Val Leu Lys Leu Pro Thr Ser Thr Ala Thr Ile Val Val
    415                 420                 425

cac gtg gag gat gtg aat gag gca cct gtg ttt gtc cca ccc tcc aaa     1405
His Val Glu Asp Val Asn Glu Ala Pro Val Phe Val Pro Pro Ser Lys
430                 435                 440                 445

gtc gtt gag gtc cag gag ggc atc ccc act ggg gag cct gtg tgt gtc     1453
Val Val Glu Val Gln Glu Gly Ile Pro Thr Gly Glu Pro Val Cys Val
                450                 455                 460

tac act gca gaa gac cct gac aag gag aat caa aag atc agc tac cgc     1501
Tyr Thr Ala Glu Asp Pro Asp Lys Glu Asn Gln Lys Ile Ser Tyr Arg
            465                 470                 475

atc ctg aga gac cca gca ggg tgg cta gcc atg gac cca gac agt ggg     1549
Ile Leu Arg Asp Pro Ala Gly Trp Leu Ala Met Asp Pro Asp Ser Gly
        480                 485                 490

cag gtc aca gct gtg ggc acc ctc gac cgt gag gat gag cag ttt gtg     1597
Gln Val Thr Ala Val Gly Thr Leu Asp Arg Glu Asp Glu Gln Phe Val
    495                 500                 505

agg aac aac atc tat gaa gtc atg gtc ttg gcc atg gac aat gga agc     1645
Arg Asn Asn Ile Tyr Glu Val Met Val Leu Ala Met Asp Asn Gly Ser
510                 515                 520                 525
```

```
cct ccc acc act ggc acg gga acc ctt ctg cta aca ctg att gat gtc      1693
Pro Pro Thr Thr Gly Thr Gly Thr Leu Leu Leu Thr Leu Ile Asp Val
                530                 535                 540

aat gac cat ggc cca gtc cct gag ccc cgt cag atc acc atc tgc aac      1741
Asn Asp His Gly Pro Val Pro Glu Pro Arg Gln Ile Thr Ile Cys Asn
            545                 550                 555

caa agc cct gtg cgc cag gtg ctg aac atc acg gac aag gac ctg tct      1789
Gln Ser Pro Val Arg Gln Val Leu Asn Ile Thr Asp Lys Asp Leu Ser
        560                 565                 570

ccc cac acc tcc cct ttc cag gcc cag ctc aca gat gac tca gac atc      1837
Pro His Thr Ser Pro Phe Gln Ala Gln Leu Thr Asp Asp Ser Asp Ile
    575                 580                 585

tac tgg acg gca gag gtc aac gag gaa ggt gac aca gtg gtc ttg tcc      1885
Tyr Trp Thr Ala Glu Val Asn Glu Glu Gly Asp Thr Val Val Leu Ser
590                 595                 600                 605

ctg aag aag ttc ctg aag cag gat aca tat gac gtg cac ctt tct ctg      1933
Leu Lys Lys Phe Leu Lys Gln Asp Thr Tyr Asp Val His Leu Ser Leu
                610                 615                 620

tct gac cat ggc aac aaa gag cag ctg acg gtg atc agg gcc act gtg      1981
Ser Asp His Gly Asn Lys Glu Gln Leu Thr Val Ile Arg Ala Thr Val
            625                 630                 635

tgc gac tgc cat ggc cat gtc gaa acc tgc cct gga ccc tgg aag gga      2029
Cys Asp Cys His Gly His Val Glu Thr Cys Pro Gly Pro Trp Lys Gly
        640                 645                 650

ggt ttc atc ctc cct gtg ctg ggg gct gtc ctg gct ctg ctg ttc ctc      2077
Gly Phe Ile Leu Pro Val Leu Gly Ala Val Leu Ala Leu Leu Phe Leu
    655                 660                 665

ctg ctg gtg ctg ctt ttg ttg gtg aga aag aag cgg aag atc aag gag      2125
Leu Leu Val Leu Leu Leu Leu Val Arg Lys Lys Arg Lys Ile Lys Glu
670                 675                 680                 685

ccc ctc cta ctc cca gaa gat gac acc cgt gac aac gtc ttc tac tat      2173
Pro Leu Leu Leu Pro Glu Asp Asp Thr Arg Asp Asn Val Phe Tyr Tyr
                690                 695                 700

ggc gaa gag ggg ggt ggc gaa gag gac cag gac tat gac atc acc cag      2221
Gly Glu Glu Gly Gly Gly Glu Glu Asp Gln Asp Tyr Asp Ile Thr Gln
            705                 710                 715

ctc cac cga ggt ctg gag gcc agg ccg gag gtg gtt ctc cgc aat gac      2269
Leu His Arg Gly Leu Glu Ala Arg Pro Glu Val Val Leu Arg Asn Asp
        720                 725                 730

gtg gca cca acc atc atc ccg aca ccc atg tac cgt cct cgg cca gcc      2317
Val Ala Pro Thr Ile Ile Pro Thr Pro Met Tyr Arg Pro Arg Pro Ala
    735                 740                 745

aac cca gat gaa atc ggc aac ttt ata att gag aac ctg aag gcg gct      2365
Asn Pro Asp Glu Ile Gly Asn Phe Ile Ile Glu Asn Leu Lys Ala Ala
750                 755                 760                 765
```

```
aac aca gac ccc aca gcc ccg ccc tac gac acc ctc ttg gtg ttc gac      2413
Asn Thr Asp Pro Thr Ala Pro Pro Tyr Asp Thr Leu Leu Val Phe Asp
                770                 775                 780

tat gag ggc agc ggc tcc gac gcc gcg tcc ctg agc tcc ctc acc tcc      2461
Tyr Glu Gly Ser Gly Ser Asp Ala Ala Ser Leu Ser Ser Leu Thr Ser
            785                 790                 795

tcc gcc tcc gac caa gac caa gat tac gat tat ctg aac gag tgg ggc      2509
Ser Ala Ser Asp Gln Asp Gln Asp Tyr Asp Tyr Leu Asn Glu Trp Gly
        800                 805                 810

agc cgc ttc aag aag ctg gca gac atg tac ggt ggc ggg gag gac gac      2557
Ser Arg Phe Lys Lys Leu Ala Asp Met Tyr Gly Gly Gly Glu Asp Asp
    815                 820                 825

tag gcggcctgcc tgcagggctg gggaccaaac gtcaggccac agagcatctc           2610

caaggggtct cagttccccc ttcagctgag gacttcggag cttgtcagga agtggccgta    2670
gcaacttggc ggagacaggc tatgagtctg acgttagagt ggttgcttcc ttagcctttc    2730
aggatggagg aatgtgggca gtttgacttc agcactgaaa acctctccac ctgggccagg    2790
gttgcctcag aggccaagtt tccagaagcc tcttacctgc cgtaaaatgc tcaaccctgt    2850
gtcctgggcc tgggcctgct gtgactgacc tacagtggac tttctctctg gaatggaacc    2910
ttcttaggcc tcctggtgca acttaatttt ttttttaat gctatcttca aaacgttaga     2970
gaaagttctt caaaagtgca gcccagagct gctgggccca ctggccgtcc tgcatttctg    3030
gtttccagac cccaatgcct cccattcgga tggatctctg cgtttttata ctgagtgtgc    3090
ctaggttgcc ccttattttt tattttccct gttgcgttgc tatagatgaa gggtgaggac    3150
aatcgtgtat atgtactaga actttttat taaagaaact tttcccagaa aaaaa          3205
```

<210> 4
<211> 829
<212> PRT
<213> Homo sapiens

<400> 4

```
Met Gly Leu Pro Arg Gly Pro Leu Ala Ser Leu Leu Leu Leu Gln Val
1               5                  10                  15

Cys Trp Leu Gln Cys Ala Ala Ser Glu Pro Cys Arg Ala Val Phe Arg
            20                  25                  30

Glu Ala Glu Val Thr Leu Glu Ala Gly Gly Ala Glu Gln Glu Pro Gly
        35                  40                  45

Gln Ala Leu Gly Lys Val Phe Met Gly Cys Pro Gly Gln Glu Pro Ala
    50                  55                  60

Leu Phe Ser Thr Asp Asn Asp Asp Phe Thr Val Arg Asn Gly Glu Thr
65                  70                  75                  80

Val Gln Glu Arg Arg Ser Leu Lys Glu Arg Asn Pro Leu Lys Ile Phe
                85                  90                  95

Pro Ser Lys Arg Ile Leu Arg Arg His Lys Arg Asp Trp Val Val Ala
            100                 105                 110

Pro Ile Ser Val Pro Glu Asn Gly Lys Gly Pro Phe Pro Gln Arg Leu
        115                 120                 125
```

```
Asn Gln Leu Lys Ser Asn Lys Asp Arg Asp Thr Lys Ile Phe Tyr Ser
    130                 135                 140

Ile Thr Gly Pro Gly Ala Asp Ser Pro Pro Glu Gly Val Phe Ala Val
145                 150                 155                 160

Glu Lys Glu Thr Gly Trp Leu Leu Leu Asn Lys Pro Leu Asp Arg Glu
                165                 170                 175

Glu Ile Ala Lys Tyr Glu Leu Phe Gly His Ala Val Ser Glu Asn Gly
            180                 185                 190

Ala Ser Val Glu Asp Pro Met Asn Ile Ser Ile Ile Val Thr Asp Gln
        195                 200                 205

Asn Asp His Lys Pro Lys Phe Thr Gln Asp Thr Phe Arg Gly Ser Val
    210                 215                 220

Leu Glu Gly Val Leu Pro Gly Thr Ser Val Met Gln Val Thr Ala Thr
225                 230                 235                 240

Asp Glu Asp Asp Ala Ile Tyr Thr Tyr Asn Gly Val Val Ala Tyr Ser
                245                 250                 255

Ile His Ser Gln Glu Pro Lys Asp Pro His Asp Leu Met Phe Thr Ile
            260                 265                 270

His Arg Ser Thr Gly Thr Ile Ser Val Ile Ser Ser Gly Leu Asp Arg
        275                 280                 285

Glu Lys Val Pro Glu Tyr Thr Leu Thr Ile Gln Ala Thr Asp Met Asp
    290                 295                 300

Gly Asp Gly Ser Thr Thr Thr Ala Val Ala Val Val Glu Ile Leu Asp
305                 310                 315                 320

Ala Asn Asp Asn Ala Pro Met Phe Asp Pro Gln Lys Tyr Glu Ala His
                325                 330                 335

Val Pro Glu Asn Ala Val Gly His Glu Val Gln Arg Leu Thr Val Thr
            340                 345                 350

Asp Leu Asp Ala Pro Asn Ser Pro Ala Trp Arg Ala Thr Tyr Leu Ile
        355                 360                 365

Met Gly Gly Asp Asp Gly Asp His Phe Thr Ile Thr Thr His Pro Glu
    370                 375                 380

Ser Asn Gln Gly Ile Leu Thr Thr Arg Lys Gly Leu Asp Phe Glu Ala
385                 390                 395                 400

Lys Asn Gln His Thr Leu Tyr Val Glu Val Thr Asn Glu Ala Pro Phe
                405                 410                 415

Val Leu Lys Leu Pro Thr Ser Thr Ala Thr Ile Val Val His Val Glu
            420                 425                 430

Asp Val Asn Glu Ala Pro Val Phe Val Pro Pro Ser Lys Val Val Glu
        435                 440                 445
```

Val Gln Glu Gly Ile Pro Thr Gly Glu Pro Val Cys Val Tyr Thr Ala
450 455 460

Glu Asp Pro Asp Lys Glu Asn Gln Lys Ile Ser Tyr Arg Ile Leu Arg
465 470 475 480

Asp Pro Ala Gly Trp Leu Ala Met Asp Pro Asp Ser Gly Gln Val Thr
485 490 495

Ala Val Gly Thr Leu Asp Arg Glu Asp Glu Gln Phe Val Arg Asn Asn
500 505 510

Ile Tyr Glu Val Met Val Leu Ala Met Asp Asn Gly Ser Pro Pro Thr
515 520 525

Thr Gly Thr Gly Thr Leu Leu Leu Thr Leu Ile Asp Val Asn Asp His
530 535 540

Gly Pro Val Pro Glu Pro Arg Gln Ile Thr Ile Cys Asn Gln Ser Pro
545 550 555 560

Val Arg Gln Val Leu Asn Ile Thr Asp Lys Asp Leu Ser Pro His Thr
565 570 575

Ser Pro Phe Gln Ala Gln Leu Thr Asp Asp Ser Asp Ile Tyr Trp Thr
580 585 590

Ala Glu Val Asn Glu Glu Gly Asp Thr Val Val Leu Ser Leu Lys Lys
595 600 605

Phe Leu Lys Gln Asp Thr Tyr Asp Val His Leu Ser Leu Ser Asp His
610 615 620

Gly Asn Lys Glu Gln Leu Thr Val Ile Arg Ala Thr Val Cys Asp Cys
625 630 635 640

His Gly His Val Glu Thr Cys Pro Gly Pro Trp Lys Gly Gly Phe Ile
645 650 655

Leu Pro Val Leu Gly Ala Val Leu Ala Leu Leu Phe Leu Leu Leu Val
660 665 670

Leu Leu Leu Leu Val Arg Lys Lys Arg Lys Ile Lys Glu Pro Leu Leu
675 680 685

Leu Pro Glu Asp Asp Thr Arg Asp Asn Val Phe Tyr Tyr Gly Glu Glu
690 695 700

Gly Gly Gly Glu Glu Asp Gln Asp Tyr Asp Ile Thr Gln Leu His Arg
705 710 715 720

Gly Leu Glu Ala Arg Pro Glu Val Val Leu Arg Asn Asp Val Ala Pro
725 730 735

Thr Ile Ile Pro Thr Pro Met Tyr Arg Pro Arg Pro Ala Asn Pro Asp
740 745 750

Glu Ile Gly Asn Phe Ile Ile Glu Asn Leu Lys Ala Ala Asn Thr Asp
755 760 765

```
Pro Thr Ala Pro Pro Tyr Asp Thr Leu Leu Val Phe Asp Tyr Glu Gly
    770                 775                 780

Ser Gly Ser Asp Ala Ala Ser Leu Ser Ser Leu Thr Ser Ser Ala Ser
785                 790                 795                 800

Asp Gln Asp Gln Asp Tyr Asp Tyr Leu Asn Glu Trp Gly Ser Arg Phe
                805                 810                 815

Lys Lys Leu Ala Asp Met Tyr Gly Gly Gly Glu Asp Asp
            820                 825


<210>  5
<211>  6840
<212>  DNA
<213>  Homo sapiens

<220>
<221>  CDS
<222>  (2)..(1801)
<223>

<400>  5
g gcc gct ctg gcg ccc gtc ggc tcc ccc gcc tcc cgc ggt cct agg ctg     49
  Ala Ala Leu Ala Pro Val Gly Ser Pro Ala Ser Arg Gly Pro Arg Leu
  1               5                  10                  15

gcc gcg ggc ctc cgg ctg ctc cca atg ctg ggt ttg ctg cag ttg ctg      97
Ala Ala Gly Leu Arg Leu Leu Pro Met Leu Gly Leu Leu Gln Leu Leu
            20                  25                  30

gcc gag cct ggc ctg ggc cgc gtc cat cac ctg gca ctc aag gat gat     145
Ala Glu Pro Gly Leu Gly Arg Val His His Leu Ala Leu Lys Asp Asp
        35                  40                  45

gtg agg cat aaa gtt cat ctg aac acc ttt ggc ttc ttc aag gat ggg     193
Val Arg His Lys Val His Leu Asn Thr Phe Gly Phe Phe Lys Asp Gly
    50                  55                  60

tac atg gtg gtg aat gtc agt agc ctc tca ctg aat gag cct gaa gac     241
Tyr Met Val Val Asn Val Ser Ser Leu Ser Leu Asn Glu Pro Glu Asp
65                  70                  75                  80

aag gat gtg act att gga ttt agc cta gac cgt aca aag aat gat ggc     289
Lys Asp Val Thr Ile Gly Phe Ser Leu Asp Arg Thr Lys Asn Asp Gly
                85                  90                  95

ttt tct tct tac ctg gat gaa gat gtg aat tac tgt att tta aag aaa     337
Phe Ser Ser Tyr Leu Asp Glu Asp Val Asn Tyr Cys Ile Leu Lys Lys
            100                 105                 110

cag tct gtc tct gtc acc ctt tta atc cta gac atc tcc aga agt gag     385
Gln Ser Val Ser Val Thr Leu Leu Ile Leu Asp Ile Ser Arg Ser Glu
        115                 120                 125

gta aga gta aag tct cca cca gaa gct ggt acc cag tta cca aag atc     433
Val Arg Val Lys Ser Pro Pro Glu Ala Gly Thr Gln Leu Pro Lys Ile
    130                 135                 140
```

```
atc ttc agc agg gat gag aaa gtc ctt ggt cag agc cag gag cct aat      481
Ile Phe Ser Arg Asp Glu Lys Val Leu Gly Gln Ser Gln Glu Pro Asn
145                 150                 155                 160

gtt aac cct gct tca gca ggc aac cag acc cag aag aca caa gat ggt      529
Val Asn Pro Ala Ser Ala Gly Asn Gln Thr Gln Lys Thr Gln Asp Gly
                165                 170                 175

gga aag tct aaa aga agt aca gtg gat tca aag gcc atg gga gag aaa      577
Gly Lys Ser Lys Arg Ser Thr Val Asp Ser Lys Ala Met Gly Glu Lys
            180                 185                 190

tcc ttt tct gtt cat aat aat ggt ggg gca gtg tca ttt cag ttt ttc      625
Ser Phe Ser Val His Asn Asn Gly Gly Ala Val Ser Phe Gln Phe Phe
        195                 200                 205

ttt aac atc agc act gat gac caa gaa ggc ctt tac agt ctt tat ttt      673
Phe Asn Ile Ser Thr Asp Asp Gln Glu Gly Leu Tyr Ser Leu Tyr Phe
    210                 215                 220

cat aaa tgc ctt gga aaa gaa ttg cca agt gac aag ttt aca ttc agc      721
His Lys Cys Leu Gly Lys Glu Leu Pro Ser Asp Lys Phe Thr Phe Ser
225                 230                 235                 240

ctt gat att gag atc aca gag aag aat cct gac agc tac ctc tca gca      769
Leu Asp Ile Glu Ile Thr Glu Lys Asn Pro Asp Ser Tyr Leu Ser Ala
                245                 250                 255

gga gaa att cct ctc ccc aaa tta tac atc tca atg gcc ttt ttc ttc      817
Gly Glu Ile Pro Leu Pro Lys Leu Tyr Ile Ser Met Ala Phe Phe Phe
            260                 265                 270

ttt ctt tct ggg acc atc tgg att cat atc ctt cga aaa cga cgg aat      865
Phe Leu Ser Gly Thr Ile Trp Ile His Ile Leu Arg Lys Arg Arg Asn
        275                 280                 285

gat gta ttt aaa atc cac tgg ctg atg gcg gcc ctt cct ttc acc aag      913
Asp Val Phe Lys Ile His Trp Leu Met Ala Ala Leu Pro Phe Thr Lys
    290                 295                 300

tct ctt tcc ttg gtg ttc cat gca att gac tac cac tac atc tcc tcc      961
Ser Leu Ser Leu Val Phe His Ala Ile Asp Tyr His Tyr Ile Ser Ser
305                 310                 315                 320

cag ggc ttc cct atc gaa ggc tgg gct gtt gtg tac tac ata act cac     1009
Gln Gly Phe Pro Ile Glu Gly Trp Ala Val Val Tyr Tyr Ile Thr His
                325                 330                 335

ctt ttg aaa ggg gcg cta ctc ttc atc acc att gca ctc att ggc act     1057
Leu Leu Lys Gly Ala Leu Leu Phe Ile Thr Ile Ala Leu Ile Gly Thr
            340                 345                 350

ggc tgg gct ttc att aag cac atc ctt tct gat aaa gac aaa aag atc     1105
Gly Trp Ala Phe Ile Lys His Ile Leu Ser Asp Lys Asp Lys Lys Ile
        355                 360                 365

ttc atg att gtc att cca ctc cag gtc ctg gca aat gta gcc tac atc     1153
Phe Met Ile Val Ile Pro Leu Gln Val Leu Ala Asn Val Ala Tyr Ile
    370                 375                 380
```

```
atc ata gag tcc acc gag gag ggc acg act gaa tat ggc ttg tgg aag      1201
Ile Ile Glu Ser Thr Glu Glu Gly Thr Thr Glu Tyr Gly Leu Trp Lys
385                 390                 395                 400

gac tct cta ttt ctg gtc gac ctg ttg tgt tgt ggt gcc atc ctc ttc      1249
Asp Ser Leu Phe Leu Val Asp Leu Leu Cys Cys Gly Ala Ile Leu Phe
                405                 410                 415

cca gtg gtg tgg tca atc aga cat tta caa gaa gca tca gca aca gat      1297
Pro Val Val Trp Ser Ile Arg His Leu Gln Glu Ala Ser Ala Thr Asp
            420                 425                 430

gga aaa ggt gac agc atg gga cct ctt cag cag aga gcg aat ctg aga      1345
Gly Lys Gly Asp Ser Met Gly Pro Leu Gln Gln Arg Ala Asn Leu Arg
        435                 440                 445

gca gga agt cgc ata gag tct cgc cat ttt gcc cgg gct gat ctt gaa      1393
Ala Gly Ser Arg Ile Glu Ser Arg His Phe Ala Arg Ala Asp Leu Glu
    450                 455                 460

ctc ctg gcc tct agc tgt cct cct gcc tca gtc tcc caa agg gct ggg      1441
Leu Leu Ala Ser Ser Cys Pro Pro Ala Ser Val Ser Gln Arg Ala Gly
465                 470                 475                 480

att aca gct gct att aac tta gca aag ctg aaa ctt ttc aga cat tat      1489
Ile Thr Ala Ala Ile Asn Leu Ala Lys Leu Lys Leu Phe Arg His Tyr
                485                 490                 495

tac gtc ttg att gtg tgt tac ata tac ttc act agg atc att gca ttt      1537
Tyr Val Leu Ile Val Cys Tyr Ile Tyr Phe Thr Arg Ile Ile Ala Phe
            500                 505                 510

ctc ctc aaa ctc gct gtt cca ttc cag tgg aag tgg ctc tac cag ctc      1585
Leu Leu Lys Leu Ala Val Pro Phe Gln Trp Lys Trp Leu Tyr Gln Leu
        515                 520                 525

ctg gat gaa acg gcc aca ctg gtc ttc ttt gtt cta acg ggg tat aaa      1633
Leu Asp Glu Thr Ala Thr Leu Val Phe Phe Val Leu Thr Gly Tyr Lys
    530                 535                 540

ttc cgt ccg gct tca gat aac ccc tac cta caa ctt tct cag gaa gaa      1681
Phe Arg Pro Ala Ser Asp Asn Pro Tyr Leu Gln Leu Ser Gln Glu Glu
545                 550                 555                 560

gaa gac ttg gaa atg gag tcc gtt gtg aca aca tct ggg gtg atg gaa      1729
Glu Asp Leu Glu Met Glu Ser Val Val Thr Thr Ser Gly Val Met Glu
                565                 570                 575

agt atg aag aaa gtc aag aag gtg acc aac ggc tcc gtg gag ccc cag      1777
Ser Met Lys Lys Val Lys Lys Val Thr Asn Gly Ser Val Glu Pro Gln
            580                 585                 590

ggc gag tgg gaa ggc gcc gtg tga cagagccgac cctgaggatg gcactgtcca      1831
Gly Glu Trp Glu Gly Ala Val
        595

aggaaactgt taacttattc atagtcctat tggacagcag gagcagctcc tacagtgaac    1891
tattggcacc accgacagtg acaccagggc acatggctgg agcacagtgc cgcggaaacc    1951
tgattttgta ctctctttta tggaaacgat ctgtggctgt ttagaggcag ctggatcctc    2011
tttcaggcgg gaatgggagg gcgggcacag ggaggaggag aggaagagaa aaggaagaat    2071
```

tcatttttaa tttaggtttc ttttttttctt cttcatttcg gagctctaag gtgtatgcag 2131
ttgtgacccc atgtgtgggg aagtgtagca aggacggctg gtggaggggg aaggagggtg 2191
cgaggtgtct gtctgatgct ttaggaaatg tctactgagg accctgggac ttaagaagaa 2251
gggcgggggag agtgccattg cctgtttggg agacaaaaat gaacgaaaac aggtgacttt 2311
ggaaagcaaa gtcaaaaccc agtttaggat gtagcacctg ccccaggatt cctgccctcg 2371
gctttgcccc agacccttat tccagatgct gagagtgacc aggacagcag ctcctgaggc 2431
ccagtggtct tctttccaac aggaaaagaa ggctgtgatg tcgctgtcag gatcatgccc 2491
tgtggcacag cacaggtggt gggaggtggt tttctgactg agatgttgcc tgatggatgg 2551
aaagaaatgt atttttaagt tcaaaaagca ttatcctgtg gcgttgcctg gacatccact 2611
ccctgacagc ccagagcagc actgtctggc ttcccttcat gcttgtggct ttgttgtgtt 2671
tgatcagaat tttgggggaa atggaaagtt ttcctcaagg agcagctggg ggcagaatag 2731
gtagtattta agcaaatact taagtccaag caaatcatcc ccattaaaaa gcttttcctg 2791
taggctagta ggatttctaa atagatgaat tcaacagact tggtccccat agtccaagag 2851
tatgtatgtg aagaaagtga gcatgattca acagtttcac tctcagggat tttaggatgg 2911
caaaatactt cacagaaact caatgattaa gttcccttcc acacttccag agcttgaatg 2971
aacacaggta gccacctaaa ttgagcagta ttgcaactca gagagaaaat catctgaata 3031
gtaggacaag ctcagaaggt acattgtgac tgagggctta aaaggagacc aaaacatggc 3091
cccatcaggg aagcttctta atgcttgggg ggccagctag gtagggttgc ttccaaaagc 3151
tggagcccac ccctgcctag gggttgtcag agagccacac ctgcagggga acaggtacct 3211
ccgagggtga gagtcgtggt ctctgggagt tgttttctca cctctggctt agaagggtca 3271
ggcagaaacc acaggatgtg gggtcacact cactgtccca agtttgggaa cctgaaaaag 3331
tctccattca gaacatggtt gttctccctg tcccatgcta tcttatcttc ctaaatgact 3391
aatgaggaag cgggtgttct ttttctgcac tttgattcgc catctgggtt ctgtagggtg 3451
ctctgaaggt gtgatctgcc ttctggctga tgtggaggaa gagcaagcgc cttcccaggc 3511
cacagctgct cacctctcgg cagatatttt aggcaagcat ccgtgtgtct tcccatcttc 3571
aggagaaagg taaatgcacc ctaagtgttc acttctggac ctttttcaag ttcacttggg 3631
actgtgtgac agaagggagt tggagggagg atgggaatat ttttaacact ttgttttcct 3691
gtgcagaaac ataataccag ttttcgcaga aatgtgtctc aatctgtgac taccaaagcc 3751
ctcctcagtc cttccctcag agggacacat ttgctgtttc tcccgcaagc agatgttgtg 3811
gatgaggcga tagactcctt ggcaagaacg aaaggtgtga tgaaacctcc ctgctcggaa 3871
gggtctccgt ggaggtgtcc tcatttcaca tgctgggttt tgcaagcgag gaagccaggc 3931
agtggaggaa ctagagagag gcaggcgtgt gtgtggacaa gcgctggagc cgcagccctc 3991
agactggcac gggaacgcca gcgttgggtg ttcagattcc acgcgtatgt ctgggctcac 4051
tcacagcatg gccgagtgtc tgcagtgctg gtcctgaccc ttccagagca gcagtggaca 4111
gatgagataa gactgtttca gaaacaaaga tggccacagc cttcctaaca agcaggtcat 4171
ctggccatgt ctgtattgta actggtaaaa ggcttcaagt cagattgatg atcaagaaaa 4231
gtcaaaaccc cagcccaaga ttgggaaagc aggtggtggt tccaagcttt taaaaaatta 4291
ttgaagctct ccatcctgtt ctgtgagtgt gtcttctctt tctccttcac gtcatagccg 4351
tgacccaccg ttcatctctg ctcttgcgta aagatgaccg atggagtcca aagccaagtg 4411
gcttcaccag ctgacaagcc accctcctgc agcctgagtt tcacagtcca ctgggttcgt 4471
tgtcatgcgg tgtttgaatg gttaagccct tgcagtattt cagatcgggc aaaaaatatc 4531
ggatgcacat agcagaacca ttggtggtat ttatagcttt gctttgtact cctcactgtt 4591
tctgcctacg caaaatatcc atgtttcctc tgagaaatct gttgtggact gaaagcgctg 4651
ctggctgtga aatttaataa agtgtgtatg ctttgctaga aaattatttc ttggacaata 4711
ggaacagtca ttgatctgta aatcctggct cttaacagtg agtggccaag gacttgatca 4771
gcccatttct tggtccctca gtgctttaaa atttaagtag cactgcattt tgtaatgttg 4831
aatatgactc tagtgacttg taggaggcac ttgtgaggag atgcttgctt cagtgtaaaa 4891
gatgctcatg gcctgagtca gttgagtttt ctttcaagaa accacttcag agtgaaatat 4951
ccagggtttc cccgccctgg acatgtccag cctgcccagg cagcacacag ccctgtaagt 5011
ccacctcgtg tgggtgagat ttcctcctgc gtgatgacct catcgccatc tctgctgtct 5071
cattccacag cctccctccc tcttctctcc tcctctgccc tcgcccttcc cccttcccca 5131
tcccctcccc ctcctcctct gccctcgccc ttaccccctcc cccttccccc tccgctcctc 5191
ctccctcctc cacctctttc tcctcctcct tccctcctcc tccctcctct tcccttctct 5251
gccatctttc tccccgtgcc tattgatccc acataggctc attctgggta caccggctaa 5311
aggctttggt gcattgcagc gttttctccc agcagctgtg tgaaagatgc attttctaag 5371
ctaaggagaa ttttctcaag agtggcatac tcatgccaaa tattattgct ctgggccata 5431
taggctggtc ttcctccaca ctaaaatggg tgtcttgttt tggtacttaa aacagtctac 5491
tccaggcatc cagtccttac agaccaagga agagcatagc gatgcctgtt ggaattgcag 5551
atgcattctg gccttctccc ccgtcctgaa acattttctt tgaggaaggc tcttagaaca 5611
ttagatagtc tgctgaggtt gttggcccag ctccatacac ccagtagaac agtggaacaa 5671

```
ctcatgcttc atgctgccaa gctgctgtac ttcaaaggaa acagatctag cacactgctg   5731
caccctgct tccacactcc acacttcacc ccgctgcttt tctctgaccc gcccctggcc   5791
ttgtaagact cacgtaagct aagtccagga tgcctgtggc ctgcggcttg attcttccct   5851
ttaggattca gcaagttaat ggcttcctcg ctatagaagt gagactttga cttgatgcct   5911
cttggtatat caaaaagata ttcatccaga aagtaccaaa tgttctgaaa gacccgctct   5971
tcactccagt tttccctagg gtgtttctgg cagggcgttt ttaaaaggca tctacctgag   6031
ttgacgctaa tacttgtcac cacctggaac gtagttatcg gtcggcaggc tgaacatact   6091
ccagattccc cagaggccac ttctgtagcc cagcgatgca tctgagcctc tctgcgtggt   6151
ttatgcttga aaaatagata atgcttttag atggttcact gccaggccat gggccccaca   6211
catctcaggc cctgtgtgag ggagcacact gagatggtgc aggagtgaat gggcatggct   6271
tggcctcgct acctcgggga cctgttggag ttctggcagc agggtgtctg caggtgggac   6331
ggcgttctgg gcagagtcag aatggtcaga atgaaacaga acagccaact cacccacagg   6391
acagcttatt ttgaggcaag gttttggatt ttggaggaag cagccagatg aggcggtgag   6451
cctccagaag gtcagccttt ggagcacgta agatactgtt acagggtcca gaaatcgtgt   6511
tcacatgggg gctttgactc ttcaaacagc ttttgcagat cgtaaattgc atttgcctag   6571
tcgtgtgacc tcaaaagaag tcagacatat ttaatccaga aatagtttcg tttgagggag   6631
ggcttgcagg tctgtaaata gcatttgctt tcctggttag agattgggat gcagaaggag   6691
ttttcagtat tttttttaaa acactaatga tcattgaaga gtatttatgt aaacatacaa   6751
cgtataatgg gtgggggatc cgatcatggt gatgtacggg gtgaattctc ttgccgtgtt   6811
gcaaatgtgt aaaataaaga ttatctggc                                     6840
```

<210> 6
<211> 599
<212> PRT
<213> Homo sapiens

<400> 6

```
Ala Ala Leu Ala Pro Val Gly Ser Pro Ala Ser Arg Gly Pro Arg Leu
1               5                  10                  15

Ala Ala Gly Leu Arg Leu Leu Pro Met Leu Gly Leu Leu Gln Leu Leu
            20                  25                  30

Ala Glu Pro Gly Leu Gly Arg Val His His Leu Ala Leu Lys Asp Asp
        35                  40                  45

Val Arg His Lys Val His Leu Asn Thr Phe Gly Phe Phe Lys Asp Gly
    50                  55                  60

Tyr Met Val Val Asn Val Ser Ser Leu Ser Leu Asn Glu Pro Glu Asp
65                  70                  75                  80

Lys Asp Val Thr Ile Gly Phe Ser Leu Asp Arg Thr Lys Asn Asp Gly
                85                  90                  95

Phe Ser Ser Tyr Leu Asp Glu Asp Val Asn Tyr Cys Ile Leu Lys Lys
            100                 105                 110

Gln Ser Val Ser Val Thr Leu Leu Ile Leu Asp Ile Ser Arg Ser Glu
        115                 120                 125

Val Arg Val Lys Ser Pro Pro Glu Ala Gly Thr Gln Leu Pro Lys Ile
    130                 135                 140

Ile Phe Ser Arg Asp Glu Lys Val Leu Gly Gln Ser Gln Glu Pro Asn
145                 150                 155                 160

Val Asn Pro Ala Ser Ala Gly Asn Gln Thr Gln Lys Thr Gln Asp Gly
                165                 170                 175
```

Gly Lys Ser Lys Arg Ser Thr Val Asp Ser Lys Ala Met Gly Glu Lys
180 185 190

Ser Phe Ser Val His Asn Asn Gly Gly Ala Val Ser Phe Gln Phe Phe
195 200 205

Phe Asn Ile Ser Thr Asp Asp Gln Glu Gly Leu Tyr Ser Leu Tyr Phe
210 215 220

His Lys Cys Leu Gly Lys Glu Leu Pro Ser Asp Lys Phe Thr Phe Ser
225 230 235 240

Leu Asp Ile Glu Ile Thr Glu Lys Asn Pro Asp Ser Tyr Leu Ser Ala
245 250 255

Gly Glu Ile Pro Leu Pro Lys Leu Tyr Ile Ser Met Ala Phe Phe Phe
260 265 270

Phe Leu Ser Gly Thr Ile Trp Ile His Ile Leu Arg Lys Arg Arg Asn
275 280 285

Asp Val Phe Lys Ile His Trp Leu Met Ala Ala Leu Pro Phe Thr Lys
290 295 300

Ser Leu Ser Leu Val Phe His Ala Ile Asp Tyr His Tyr Ile Ser Ser
305 310 315 320

Gln Gly Phe Pro Ile Glu Gly Trp Ala Val Val Tyr Tyr Ile Thr His
325 330 335

Leu Leu Lys Gly Ala Leu Leu Phe Ile Thr Ile Ala Leu Ile Gly Thr
340 345 350

Gly Trp Ala Phe Ile Lys His Ile Leu Ser Asp Lys Asp Lys Lys Ile
355 360 365

Phe Met Ile Val Ile Pro Leu Gln Val Leu Ala Asn Val Ala Tyr Ile
370 375 380

Ile Ile Glu Ser Thr Glu Glu Gly Thr Thr Glu Tyr Gly Leu Trp Lys
385 390 395 400

Asp Ser Leu Phe Leu Val Asp Leu Leu Cys Cys Gly Ala Ile Leu Phe
405 410 415

Pro Val Val Trp Ser Ile Arg His Leu Gln Glu Ala Ser Ala Thr Asp
420 425 430

Gly Lys Gly Asp Ser Met Gly Pro Leu Gln Gln Arg Ala Asn Leu Arg
435 440 445

Ala Gly Ser Arg Ile Glu Ser Arg His Phe Ala Arg Ala Asp Leu Glu
450 455 460

Leu Leu Ala Ser Ser Cys Pro Pro Ala Ser Val Ser Gln Arg Ala Gly
465 470 475 480

Ile Thr Ala Ala Ile Asn Leu Ala Lys Leu Lys Leu Phe Arg His Tyr
485 490 495

```
Tyr Val Leu Ile Val Cys Tyr Ile Tyr Phe Thr Arg Ile Ile Ala Phe
            500                 505                 510

Leu Leu Lys Leu Ala Val Pro Phe Gln Trp Lys Trp Leu Tyr Gln Leu
        515                 520                 525

Leu Asp Glu Thr Ala Thr Leu Val Phe Phe Val Leu Thr Gly Tyr Lys
    530                 535                 540

Phe Arg Pro Ala Ser Asp Asn Pro Tyr Leu Gln Leu Ser Gln Glu Glu
545                 550                 555                 560

Glu Asp Leu Glu Met Glu Ser Val Val Thr Thr Ser Gly Val Met Glu
                565                 570                 575

Ser Met Lys Lys Val Lys Lys Val Thr Asn Gly Ser Val Glu Pro Gln
            580                 585                 590

Gly Glu Trp Glu Gly Ala Val
        595


<210>  7
<211>  3468
<212>  DNA
<213>  Homo sapiens

<220>
<221>  CDS
<222>  (43)..(3003)
<223>

<400>  7
ctgggataga agcggcagga gcagcgttgg caccggcgaa cc atg gct ggg att      54
                                                Met Ala Gly Ile
                                                1

ttc tat ttc gcc cta ttt tcg tgt ctc ttc ggg att tgc gac gct gtc      102
Phe Tyr Phe Ala Leu Phe Ser Cys Leu Phe Gly Ile Cys Asp Ala Val
5                   10                  15                  20

aca ggt tcc agg gta tac ccc gcg aat gaa gtt acc tta ttg gat tcc      150
Thr Gly Ser Arg Val Tyr Pro Ala Asn Glu Val Thr Leu Leu Asp Ser
                25                  30                  35

aga tct gtt cag gga gaa ctt ggg tgg ata gca agc cct ctg gaa gga      198
Arg Ser Val Gln Gly Glu Leu Gly Trp Ile Ala Ser Pro Leu Glu Gly
            40                  45                  50

ggg tgg gag gaa gtg agt atc atg gat gaa aaa aat aca cca atc cga      246
Gly Trp Glu Glu Val Ser Ile Met Asp Glu Lys Asn Thr Pro Ile Arg
        55                  60                  65

acc tac caa gtg tgc aat gtg atg gaa ccc agc cag aat aac tgg cta      294
Thr Tyr Gln Val Cys Asn Val Met Glu Pro Ser Gln Asn Asn Trp Leu
    70                  75                  80

cga act gat tgg atc acc cga gaa ggg gct cag agg gtg tat att gag      342
Arg Thr Asp Trp Ile Thr Arg Glu Gly Ala Gln Arg Val Tyr Ile Glu
```

```
85                  90                  95                  100

att aaa ttc acc ttg agg gac tgc aat agt ctt ccg ggc gtc atg ggg      390
Ile Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu Pro Gly Val Met Gly
                    105                 110                 115

act tgc aag gag acg ttt aac ctg tac tac tat gaa tca gac aac gac      438
Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu Ser Asp Asn Asp
                120                 125                 130

aaa gag cgt ttc atc aga gag aac cag ttt gtc aaa att gac acc att      486
Lys Glu Arg Phe Ile Arg Glu Asn Gln Phe Val Lys Ile Asp Thr Ile
        135                 140                 145

gct gct gat gag agc ttc acc caa gtg gac att ggt gac aga atc atg      534
Ala Ala Asp Glu Ser Phe Thr Gln Val Asp Ile Gly Asp Arg Ile Met
    150                 155                 160

aag ctg aac acc gag atc cgg gat gta ggg cca tta agc aaa aag ggg      582
Lys Leu Asn Thr Glu Ile Arg Asp Val Gly Pro Leu Ser Lys Lys Gly
165                 170                 175                 180

ttt tac ctg gct ttt cag gat gtg ggg gcc tgc atc gcc ctg gta tca      630
Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Ile Ala Leu Val Ser
                    185                 190                 195

gtc cgt gtg ttc tat aaa aag tgt cca ctc aca gtc cgc aat ctg gcc      678
Val Arg Val Phe Tyr Lys Lys Cys Pro Leu Thr Val Arg Asn Leu Ala
                200                 205                 210

cag ttt cct gac acc atc aca ggg gct gat acg tct tcc ctg gtg gaa      726
Gln Phe Pro Asp Thr Ile Thr Gly Ala Asp Thr Ser Ser Leu Val Glu
        215                 220                 225

gtt cga ggc tcc tgt gtc aac aac tca gaa gag aaa gat gtg cca aaa      774
Val Arg Gly Ser Cys Val Asn Asn Ser Glu Glu Lys Asp Val Pro Lys
    230                 235                 240

atg tac tgt ggg gca gat ggt gaa tgg ctg gta ccc att ggc aac tgc      822
Met Tyr Cys Gly Ala Asp Gly Glu Trp Leu Val Pro Ile Gly Asn Cys
245                 250                 255                 260

cta tgc aac gct ggg cat gag gag cgg agc gga gaa tgc caa gct tgc      870
Leu Cys Asn Ala Gly His Glu Glu Arg Ser Gly Glu Cys Gln Ala Cys
                    265                 270                 275

aaa att gga tat tac aag gct ctc tcc acg gat gcc acc tgt gcc aag      918
Lys Ile Gly Tyr Tyr Lys Ala Leu Ser Thr Asp Ala Thr Cys Ala Lys
                280                 285                 290

tgc cca ccc cac agc tac tct gtc tgg gaa gga gcc acc tcg tgc acc      966
Cys Pro Pro His Ser Tyr Ser Val Trp Glu Gly Ala Thr Ser Cys Thr
        295                 300                 305

tgt gac cga ggc ttt ttc aga gct gac aac gat gct gcc tct atg ccc     1014
Cys Asp Arg Gly Phe Phe Arg Ala Asp Asn Asp Ala Ala Ser Met Pro
    310                 315                 320

tgc acc cgt cca cca tct gct ccc ctg aac ttg att tca aat gtc aac     1062
Cys Thr Arg Pro Pro Ser Ala Pro Leu Asn Leu Ile Ser Asn Val Asn
```

```
325                 330                 335                 340

gag aca tct gtg aac ttg gaa tgg agt agc cct cag aat aca ggt ggc      1110
Glu Thr Ser Val Asn Leu Glu Trp Ser Ser Pro Gln Asn Thr Gly Gly
                345                 350                 355

cgc cag gac att tcc tat aat gtg gta tgc aag aaa tgt gga gct ggt      1158
Arg Gln Asp Ile Ser Tyr Asn Val Val Cys Lys Lys Cys Gly Ala Gly
            360                 365                 370

gac ccc agc aag tgc cga ccc tgt gga agt ggg gtc cac tac acc cca      1206
Asp Pro Ser Lys Cys Arg Pro Cys Gly Ser Gly Val His Tyr Thr Pro
        375                 380                 385

cag cag aat ggc ttg aag acc acc aaa gtc tcc atc act gac ctc cta      1254
Gln Gln Asn Gly Leu Lys Thr Thr Lys Val Ser Ile Thr Asp Leu Leu
    390                 395                 400

gct cat acc aat tac acc ttt gaa atc tgg gct gtg aat gga gtg tcc      1302
Ala His Thr Asn Tyr Thr Phe Glu Ile Trp Ala Val Asn Gly Val Ser
405                 410                 415                 420

aaa tat aac cct aac cca gac caa tca gtt tct gtc act gtg acc acc      1350
Lys Tyr Asn Pro Asn Pro Asp Gln Ser Val Ser Val Thr Val Thr Thr
                425                 430                 435

aac caa gca gca cca tca tcc att gct ttg gtc cag gct aaa gaa gtc      1398
Asn Gln Ala Ala Pro Ser Ser Ile Ala Leu Val Gln Ala Lys Glu Val
            440                 445                 450

aca aga tac agt gtg gca ctg gct tgg ctg gaa cca gat cgg ccc aat      1446
Thr Arg Tyr Ser Val Ala Leu Ala Trp Leu Glu Pro Asp Arg Pro Asn
        455                 460                 465

ggg gta atc ctg gaa tat gaa gtc aag tat tat gag aag gat cag aat      1494
Gly Val Ile Leu Glu Tyr Glu Val Lys Tyr Tyr Glu Lys Asp Gln Asn
    470                 475                 480

gag cga agc tat cgt ata gtt cgg aca gct gcc agg aac aca gat atc      1542
Glu Arg Ser Tyr Arg Ile Val Arg Thr Ala Ala Arg Asn Thr Asp Ile
485                 490                 495                 500

aaa ggc ctg aac cct ctc act tcc tat gtt ttc cac gtg cga gcc agg      1590
Lys Gly Leu Asn Pro Leu Thr Ser Tyr Val Phe His Val Arg Ala Arg
                505                 510                 515

aca gca gct ggc tat gga gac ttc agt gag ccc ttg gag gtt aca acc      1638
Thr Ala Ala Gly Tyr Gly Asp Phe Ser Glu Pro Leu Glu Val Thr Thr
            520                 525                 530

aac aca gtg cct tcc cgg atc att gga gat ggg gct aac tcc aca gtc      1686
Asn Thr Val Pro Ser Arg Ile Ile Gly Asp Gly Ala Asn Ser Thr Val
        535                 540                 545

ctt ctg gtc tct gtc tcg ggc agt gtg gtg ctg gtg gta att ctc att      1734
Leu Leu Val Ser Val Ser Gly Ser Val Val Leu Val Val Ile Leu Ile
    550                 555                 560

gca gct ttt gtc atc agc cgg aga cgg agt aaa tac agt aaa gcc aaa      1782
Ala Ala Phe Val Ile Ser Arg Arg Arg Ser Lys Tyr Ser Lys Ala Lys
```

```
565                 570                 575                 580

caa gaa gcg gat gaa gag aaa cat ttg aat caa ggt gta aga aca tat     1830
Gln Glu Ala Asp Glu Glu Lys His Leu Asn Gln Gly Val Arg Thr Tyr
                585                 590                 595

gtg gac ccc ttt acg tac gaa gat ccc aac caa gca gtg cga gag ttt     1878
Val Asp Pro Phe Thr Tyr Glu Asp Pro Asn Gln Ala Val Arg Glu Phe
            600                 605                 610

gcc aaa gaa att gac gca tcc tgc att aag att gaa aaa gtt ata gga     1926
Ala Lys Glu Ile Asp Ala Ser Cys Ile Lys Ile Glu Lys Val Ile Gly
        615                 620                 625

gtt ggt gaa ttt ggt gag gta tgc agt ggg cgt ctc aaa gtg cct ggc     1974
Val Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Val Pro Gly
    630                 635                 640

aag aga gag atc tgt gtg gct atc aag act ctg aaa gct ggt tat aca     2022
Lys Arg Glu Ile Cys Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr
645                 650                 655                 660

gac aaa cag agg aga gac ttc ctg agt gag gcc agc atc atg gga cag     2070
Asp Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly Gln
                665                 670                 675

ttt gac cat ccg aac atc att cac ttg gaa ggc gtg gtc act aaa tgt     2118
Phe Asp His Pro Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Cys
            680                 685                 690

aaa cca gta atg atc ata aca gag tac atg gag aat ggc tcc ttg gat     2166
Lys Pro Val Met Ile Ile Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp
        695                 700                 705

gca ttc ctc agg aaa aat gat ggc aga ttt aca gtc att cag ctg gtg     2214
Ala Phe Leu Arg Lys Asn Asp Gly Arg Phe Thr Val Ile Gln Leu Val
    710                 715                 720

ggc atg ctt cgt ggc att ggg tct ggg atg aag tat tta tct gat atg     2262
Gly Met Leu Arg Gly Ile Gly Ser Gly Met Lys Tyr Leu Ser Asp Met
725                 730                 735                 740

agc tat gtg cat cgt gat ctg gcc gca cgg aac atc ctg gtg aac agc     2310
Ser Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser
                745                 750                 755

aac ttg gtc tgc aaa gtg tct gat ttt ggc atg tcc cga gtg ctt gag     2358
Asn Leu Val Cys Lys Val Ser Asp Phe Gly Met Ser Arg Val Leu Glu
            760                 765                 770

gat gat ccg gaa gca gct tac acc acc agg ggt ggc aag att cct atc     2406
Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile
        775                 780                 785

cgg tgg act gcg cca gaa gca att gcc tat cgt aaa ttc aca tca gca     2454
Arg Trp Thr Ala Pro Glu Ala Ile Ala Tyr Arg Lys Phe Thr Ser Ala
    790                 795                 800

agt gat gta tgg agc tat gga atc gtt atg tgg gaa gtg atg tcg tac     2502
Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Tyr
```

```
805                 810                 815                 820

ggg gag agg ccc tat tgg gat atg tcc aat caa gat gtg att aaa gcc     2550
Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile Lys Ala
                825                 830                 835

att gag gaa ggc tat cgg tta ccc cct cca atg gac tgc ccc att gcg     2598
Ile Glu Glu Gly Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro Ile Ala
            840                 845                 850

ctc cac cag ctg atg cta gac tgc tgg cag aag gag agg agc gac agg     2646
Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ser Asp Arg
        855                 860                 865

cct aaa ttt ggg cag att gtc aac atg ttg gac aaa ctc atc cgc aac     2694
Pro Lys Phe Gly Gln Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn
    870                 875                 880

ccc aac agc ttg aag agg aca ggg acg gag agc tcc aga cct aac act     2742
Pro Asn Ser Leu Lys Arg Thr Gly Thr Glu Ser Ser Arg Pro Asn Thr
885                 890                 895                 900

gcc ttg ttg gat cca agc tcc cct gaa ttc tct gct gtg gta tca gtg     2790
Ala Leu Leu Asp Pro Ser Ser Pro Glu Phe Ser Ala Val Val Ser Val
                905                 910                 915

ggc gat tgg ctc cag gcc att aaa atg gac cgg tat aag gat aac ttc     2838
Gly Asp Trp Leu Gln Ala Ile Lys Met Asp Arg Tyr Lys Asp Asn Phe
            920                 925                 930

aca gct gct ggt tat acc aca cta gag gct gtg gtg cac gtg aac cag     2886
Thr Ala Ala Gly Tyr Thr Thr Leu Glu Ala Val Val His Val Asn Gln
        935                 940                 945

gag gac ctg gca aga att ggt atc aca gcc atc acg cac cag aat aag     2934
Glu Asp Leu Ala Arg Ile Gly Ile Thr Ala Ile Thr His Gln Asn Lys
    950                 955                 960

att ttg agc agt gtc cag gca atg cga acc caa atg cag cag atg cac     2982
Ile Leu Ser Ser Val Gln Ala Met Arg Thr Gln Met Gln Gln Met His
965                 970                 975                 980

ggc aga atg gtt ccc gtc tga gccagtactg aataaactca aaactcttga        3033
Gly Arg Met Val Pro Val
                985

aattagttta cctcatccat gcactttaat tgaagaactg cacttttttt acttcgtctt   3093
cgccctctga aattaaagaa atgaaaaaaa aaaacaatat ctgcagcgtt gcttggtgca   3153
cagattgctg aaactgtggg gcttacagaa atgactgccg gtcatttgaa tgagacctgg   3213
aacaaatcgt ttctcagaag tacttttctg ttcatcacca gtctgtaaaa tacatgtacc   3273
tatagaaata gaacactgcc tctgagtttt gatgctgtat ttgctgccag acactgagct   3333
tctgagacat ccctgattct ctctccattt ggaattacaa ccattgtatt ttgtttgtgg   3393
cataaattac agtcatctgt ctttcactgg aatgaagacc atgcctagga acatttttta   3453
aggactcagc tgtgg                                                    3468
```

<210> 8
<211> 986
<212> PRT
<213> Homo sapiens

<400> 8

```
Met Ala Gly Ile Phe Tyr Phe Ala Leu Phe Ser Cys Leu Phe Gly Ile
1               5                  10                  15

Cys Asp Ala Val Thr Gly Ser Arg Val Tyr Pro Ala Asn Glu Val Thr
            20                  25                  30

Leu Leu Asp Ser Arg Ser Val Gln Gly Glu Leu Gly Trp Ile Ala Ser
        35                  40                  45

Pro Leu Glu Gly Gly Trp Glu Glu Val Ser Ile Met Asp Glu Lys Asn
    50                  55                  60

Thr Pro Ile Arg Thr Tyr Gln Val Cys Asn Val Met Glu Pro Ser Gln
65                  70                  75                  80

Asn Asn Trp Leu Arg Thr Asp Trp Ile Thr Arg Glu Gly Ala Gln Arg
                85                  90                  95

Val Tyr Ile Glu Ile Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu Pro
            100                 105                 110

Gly Val Met Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu
        115                 120                 125

Ser Asp Asn Asp Lys Glu Arg Phe Ile Arg Glu Asn Gln Phe Val Lys
    130                 135                 140

Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Val Asp Ile Gly
145                 150                 155                 160

Asp Arg Ile Met Lys Leu Asn Thr Glu Ile Arg Asp Val Gly Pro Leu
                165                 170                 175

Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Ile
            180                 185                 190

Ala Leu Val Ser Val Arg Val Phe Tyr Lys Lys Cys Pro Leu Thr Val
        195                 200                 205

Arg Asn Leu Ala Gln Phe Pro Asp Thr Ile Thr Gly Ala Asp Thr Ser
    210                 215                 220

Ser Leu Val Glu Val Arg Gly Ser Cys Val Asn Asn Ser Glu Glu Lys
225                 230                 235                 240

Asp Val Pro Lys Met Tyr Cys Gly Ala Asp Gly Glu Trp Leu Val Pro
                245                 250                 255

Ile Gly Asn Cys Leu Cys Asn Ala Gly His Glu Glu Arg Ser Gly Glu
            260                 265                 270

Cys Gln Ala Cys Lys Ile Gly Tyr Tyr Lys Ala Leu Ser Thr Asp Ala
        275                 280                 285

Thr Cys Ala Lys Cys Pro Pro His Ser Tyr Ser Val Trp Glu Gly Ala
    290                 295                 300

Thr Ser Cys Thr Cys Asp Arg Gly Phe Phe Arg Ala Asp Asn Asp Ala
```

305 310 315 320

Ala Ser Met Pro Cys Thr Arg Pro Pro Ser Ala Pro Leu Asn Leu Ile
325 330 335

Ser Asn Val Asn Glu Thr Ser Val Asn Leu Glu Trp Ser Ser Pro Gln
340 345 350

Asn Thr Gly Gly Arg Gln Asp Ile Ser Tyr Asn Val Val Cys Lys Lys
355 360 365

Cys Gly Ala Gly Asp Pro Ser Lys Cys Arg Pro Cys Gly Ser Gly Val
370 375 380

His Tyr Thr Pro Gln Gln Asn Gly Leu Lys Thr Thr Lys Val Ser Ile
385 390 395 400

Thr Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu Ile Trp Ala Val
405 410 415

Asn Gly Val Ser Lys Tyr Asn Pro Asn Pro Asp Gln Ser Val Ser Val
420 425 430

Thr Val Thr Thr Asn Gln Ala Ala Pro Ser Ser Ile Ala Leu Val Gln
435 440 445

Ala Lys Glu Val Thr Arg Tyr Ser Val Ala Leu Ala Trp Leu Glu Pro
450 455 460

Asp Arg Pro Asn Gly Val Ile Leu Glu Tyr Glu Val Lys Tyr Tyr Glu
465 470 475 480

Lys Asp Gln Asn Glu Arg Ser Tyr Arg Ile Val Arg Thr Ala Ala Arg
485 490 495

Asn Thr Asp Ile Lys Gly Leu Asn Pro Leu Thr Ser Tyr Val Phe His
500 505 510

Val Arg Ala Arg Thr Ala Ala Gly Tyr Gly Asp Phe Ser Glu Pro Leu
515 520 525

Glu Val Thr Thr Asn Thr Val Pro Ser Arg Ile Ile Gly Asp Gly Ala
530 535 540

Asn Ser Thr Val Leu Leu Val Ser Val Ser Gly Ser Val Val Leu Val
545 550 555 560

Val Ile Leu Ile Ala Ala Phe Val Ile Ser Arg Arg Arg Ser Lys Tyr
565 570 575

Ser Lys Ala Lys Gln Glu Ala Asp Glu Glu Lys His Leu Asn Gln Gly
580 585 590

Val Arg Thr Tyr Val Asp Pro Phe Thr Tyr Glu Asp Pro Asn Gln Ala
595 600 605

Val Arg Glu Phe Ala Lys Glu Ile Asp Ala Ser Cys Ile Lys Ile Glu
610 615 620

Lys Val Ile Gly Val Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu

625 630 635 640

Lys Val Pro Gly Lys Arg Glu Ile Cys Val Ala Ile Lys Thr Leu Lys
645 650 655

Ala Gly Tyr Thr Asp Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser
660 665 670

Ile Met Gly Gln Phe Asp His Pro Asn Ile Ile His Leu Glu Gly Val
675 680 685

Val Thr Lys Cys Lys Pro Val Met Ile Ile Thr Glu Tyr Met Glu Asn
690 695 700

Gly Ser Leu Asp Ala Phe Leu Arg Lys Asn Asp Gly Arg Phe Thr Val
705 710 715 720

Ile Gln Leu Val Gly Met Leu Arg Gly Ile Gly Ser Gly Met Lys Tyr
725 730 735

Leu Ser Asp Met Ser Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
740 745 750

Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Met Ser
755 760 765

Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly
770 775 780

Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Tyr Arg Lys
785 790 795 800

Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu
805 810 815

Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp
820 825 830

Val Ile Lys Ala Ile Glu Glu Gly Tyr Arg Leu Pro Pro Pro Met Asp
835 840 845

Cys Pro Ile Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu
850 855 860

Arg Ser Asp Arg Pro Lys Phe Gly Gln Ile Val Asn Met Leu Asp Lys
865 870 875 880

Leu Ile Arg Asn Pro Asn Ser Leu Lys Arg Thr Gly Thr Glu Ser Ser
885 890 895

Arg Pro Asn Thr Ala Leu Leu Asp Pro Ser Ser Pro Glu Phe Ser Ala
900 905 910

Val Val Ser Val Gly Asp Trp Leu Gln Ala Ile Lys Met Asp Arg Tyr
915 920 925

Lys Asp Asn Phe Thr Ala Ala Gly Tyr Thr Thr Leu Glu Ala Val Val
930 935 940

His Val Asn Gln Glu Asp Leu Ala Arg Ile Gly Ile Thr Ala Ile Thr

945 950 955 960

His Gln Asn Lys Ile Leu Ser Ser Val Gln Ala Met Arg Thr Gln Met
965 970 975

Gln Gln Met His Gly Arg Met Val Pro Val
980 985

<210> 9
<211> 23
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence for RT-PCR

<400> 9
agaaggagac caaggacctg tat 23

<210> 10
<211> 24
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence for RT-PCR

<400> 10
agaactttat tgtcagggtc aagg 24

<210> 11
<211> 21
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence for RT-PCR

<400> 11
ctgaaggcgg ctaacacaga c 21

<210> 12
<211> 22
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence for RT-PCR

<400> 12
tacacgattg tcctcaccct tc 22

<210> 13
<211> 23
<212> DNA

<213> Artificial

<220>
<223> An artificially synthesized primer sequence for RT-PCR

<400> 13
catccacgaa actaccttca act 23

<210> 14
<211> 23
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence for RT-PCR

<400> 14
tctccttaga gagaagtggg gtg 23

<210> 15
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 15
caccgacatc aatgacaaca cacttcaaga gagtgtgttg tcattgatgt c 51

<210> 16
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 16
aaaagacatc aatgacaaca cactctcttg aagtgtgttg tcattgatgt c 51

<210> 17
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 17
caccgtctac tccaaaccta ggtttcaaga gaacctaggt ttggagtaga c 51

<210> 18
<211> 51
<212> DNA

<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 18
aaaagtctac tccaaaccta ggttctcttg aaacctaggt ttggagtaga c 51

<210> 19
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 19
caccctctt cctcaccact aggttcaaga gacctagtgg tgaggaagag g 51

<210> 20
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 20
aaaacctctt cctcaccact aggtctcttg aacctagtgg tgaggaagag g 51

<210> 21
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 21
caccggagac aggctggttg ttgttcaaga gacaacaacc agcctgtctc c 51

<210> 22
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 22
aaaaggagac aggctggttg ttgtctcttg aacaacaacc agcctgtctc c 51

<210> 23
<211> 51
<212> DNA

<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 23
cacccatctc catcatcgtg accttcaaga gaggtcacga tgatggagat g 51

<210> 24
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 24
aaaacatctc catcatcgtg acctctcttg aaggtcacga tgatggagat g 51

<210> 25
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 25
cacccatcac ggacaaggac ctgttcaaga gacaggtcct tgtccgtgat g 51

<210> 26
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 26
aaaacatcac ggacaaggac ctgtctcttg aacaggtcct tgtccgtgat g 51

<210> 27
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 27
caccgtggct ctaccagctc ctgttcaaga gacaggagct ggtagagcca c 51

<210> 28
<211> 51
<212> DNA

<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 28
aaaagtggct ctaccagctc ctgtctcttg aacaggagct ggtagagcca c 51

<210> 29
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 29
caccattccg tccggcttca gatttcaaga gaatctgaag ccggacggaa t 51

<210> 30
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 30
aaaaattccg tccggcttca gattctcttg aaatctgaag ccggacggaa t 51

<210> 31
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 31
caccgacttg gaaatggagt ccgttcaaga gacggactcc atttccaagt c 51

<210> 32
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 32
aaaagacttg gaaatggagt ccgtctcttg aacggactcc atttccaagt c 51

<210> 33
<211> 51
<212> DNA

<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 33
caccgaaagt caagaaggtg accttcaaga gaggtcacct tcttgacttt c 51

<210> 34
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 34
aaaagaaagt caagaaggtg acctctcttg aaggtcacct tcttgacttt c 51

<210> 35
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 35
cacctccgaa cctaccaagt gtgttcaaga gacacacttg gtaggttcgg a 51

<210> 36
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 36
aaaatccgaa cctaccaagt gtgtctcttg aacacacttg gtaggttcgg a 51

<210> 37
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 37
cacctcatga agctgaacac cgattcaaga gatcggtgtt cagcttcatg a 51

<210> 38
<211> 51
<212> DNA

<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 38
aaaatcatga agctgaacac cgatctcttg aatcggtgtt cagcttcatg a 51

<210> 39
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 39
caccgcagca ccatcatcca ttgttcaaga gacaatggat gatggtgctg c 51

<210> 40
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 40
aaaagcagca ccatcatcca ttgtctcttg aacaatggat gatggtgctg c 51

<210> 41
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 41
gacatcaatg acaacacact tcaagagagt gtgttgtcat tgatgtc 47

<210> 42
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 42
gtctactcca aacctaggtt tcaagagaac ctaggtttgg agtagac 47

<210> 43
<211> 47
<212> DNA

<213> Artificial

<220>
<223> siRNA hairpin design

<400> 43
cctcttcctc accactaggt tcaagagacc tagtggtgag gaagagg 47

<210> 44
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 44
ggagacaggc tggttgttgt tcaagagaca acaaccagcc tgtctcc 47

<210> 45
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 45
catctccatc atcgtgacct tcaagagagg tcacgatgat ggagatg 47

<210> 46
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 46
catcacggac aaggacctgt tcaagagaca ggtccttgtc cgtgatg 47

<210> 47
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 47
gtggctctac cagctcctgt tcaagagaca ggagctggta gagccac 47

<210> 48
<211> 47
<212> DNA

<213> Artificial

<220>
<223> siRNA hairpin design

<400> 48
attccgtccg gcttcagatt tcaagagaat ctgaagccgg acggaat 47

<210> 49
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 49
gacttggaaa tggagtccgt tcaagagacg gactccattt ccaagtc 47

<210> 50
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 50
gaaagtcaag aaggtgacct tcaagagagg tcaccttctt gactttc 47

<210> 51
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 51
tccgaaccta ccaagtgtgt tcaagagaca cacttggtag gttcgga 47

<210> 52
<211> 47
<212> DNA
<213> Artificial

<220>
<223> siRNA hairpin design

<400> 52
tcatgaagct gaacaccgat tcaagagatc ggtgttcagc ttcatga 47

<210> 53
<211> 47
<212> DNA

<213> Artificial

<220>
<223> siRNA hairpin design

<400> 53
gcagcaccat catccattgt tcaagagaca atggatgatg gtgctgc 47

<210> 54
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 54
gacatcaatg acaacacac 19

<210> 55
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 55
gtctactcca aacctaggt 19

<210> 56
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 56
cctcttcctc accactagg 19

<210> 57
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 57
ggagacaggc tggttgttg 19

<210> 58
<211> 19
<212> DNA

<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 58
catctccatc atcgtgacc 19

<210> 59
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 59
catcacggac aaggacctg 19

<210> 60
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 60
gtggctctac cagctcctg 19

<210> 61
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 61
attccgtccg gcttcagat 19

<210> 62
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 62
gacttggaaa tggagtccg 19

<210> 63
<211> 19
<212> DNA

<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 63
gaaagtcaag aaggtgacc 19

<210> 64
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 64
tccgaaccta ccaagtgtg 19

<210> 65
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 65
tcatgaagct gaacaccga 19

<210> 66
<211> 19
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized target sequence for siRNA

<400> 66
gcagcaccat catccattg 19

<210> 67
<211> 4869
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized plasmid sequence

<220>
<221> misc_feature
<222> (485)..(490)
<223> "n" indicates GAP

<400> 67

gacggatcgg gagatctccc gatcccctat ggtgcactct cagtacaatc tgctctggat 60
ccactagtaa cggccgccag tgtgctggaa ttcggcttgg ggatcagcgt ttgagtaaga 120
gcccgcgtct gaaccctccg cgccgccccg gccccagtgg aaagacgcgc aggcaaaacg 180
caccacgtga cggagcgtga ccgcgcgccg agcgcgcgcc aaggtcgggc aggaagaggg 240
cctatttccc atgattcctt catatttgca tatacgatac aaggctgtta gagagataat 300
tagaattaat ttgactgtaa acacaaagat attagtacaa aatacgtgac gtagaaagta 360
ataatttctt gggtagtttg cagttttaaa attatgtttt aaaatggact atcatatgct 420
taccgtaact tgaaagtatt tcgatttctt ggctttatat atcttgtgga aaggacgaaa 480
caccnnnnnn tttttacatc aggttgtttt tctgtttggt ttttttttta caccacgttt 540
atacgccggt gcacggttta ccactgaaaa caccttttcat ctacaggtga tatcttttaa 600
cacaaataaa atgtagtagt cctaggagac ggaatagaag gaggtggggc ctaaagccga 660
attctgcaga tatccatcac actggcggcc gctcgagtga ggcggaaaga accagctggg 720
gctctagggg gtatccccac gcgccctgta gcggcgcatt aagcgcggcg ggtgtggtgg 780
ttacgcgcag cgtgaccgct acacttgcca gcgccctagc gcccgctcct ttcgctttct 840
tcccttcctt tctcgccacg ttcgccggct ttccccgtca agctctaaat cgggggctcc 900
ctttagggtt ccgatttagt gctttacggc acctcgaccc caaaaaactt gattagggtg 960
atggttcacg tagtgggcca tcgccctgat agacggtttt tcgccctttg acgttggagt 1020
ccacgttctt taatagtgga ctcttgttcc aaactggaac aacactcaac cctatctcgg 1080
tctattcttt tgatttataa gggattttgc cgatttcggc ctattggtta aaaaatgagc 1140
tgatttaaca aaaatttaac gcgaattaat tctgtggaat gtgtgtcagt tagggtgtgg 1200
aaagtcccca ggctccccag caggcagaag tatgcaaagc atgcatctca attagtcagc 1260
aaccaggtgt ggaaagtccc caggctcccc agcaggcaga agtatgcaaa gcatgcatct 1320
caattagtca gcaaccatag tcccgccccc aactccgccc atcccgcccc taactccgcc 1380
cagttccgcc cattctccgc cccatggctg actaattttt tttatttatg cagaggccga 1440
ggccgcctct gcctctgagc tattccagaa gtagtgagga ggcttttttg gaggcctagg 1500
cttttgcaaa aagctcccgg gagcttgtat atccatttcc ggatctgatc aagagacagg 1560
atgaggatcg tttcgcatga ttgaacaaga tggattgcac gcaggttctc cggccgcttg 1620
ggtggagagg ctattcggct atgactgggc acaacagaca atcggctgct ctgatgccgc 1680
cgtgttccgg ctgtcagcgc aggggcgccc ggttcttttt gtcaagaccg acctgtccgg 1740
tgccctgaat gaactgcagg acgaggcagc gcggctatcg tggctggcca cgacgggcgt 1800
tccttgcgca gctgtgctcg acgttgtcac tgaagcggga agggactggc tgctattggg 1860
cgaagtgccg gggcaggatc tcctgtcatc tcaccttgct cctgccgaga aagtatccat 1920
catggctgat gcaatgcggc ggctgcatac gcttgatccg gctacctgcc cattcgacca 1980
ccaagcgaaa catcgcatcg agcgagcacg tactcggatg gaagccggtc ttgtcgatca 2040
ggatgatctg gacgaagagc atcaggggct cgcgccagcc gaactgttcg ccaggctcaa 2100
ggcgcgcatg cccgacggcg aggatctcgt cgtgacccat ggcgatgcct gcttgccgaa 2160
tatcatggtg gaaaatggcc gcttttctgg attcatcgac tgtggccggc tgggtgtggc 2220
ggaccgctat caggacatag cgttggctac ccgtgatatt gctgaagagc ttggcggcga 2280
atgggctgac cgcttcctcg tgctttacgg tatcgccgct cccgattcgc agcgcatcgc 2340
cttctatcgc cttcttgacg agttcttctg agcgggactc tggggttcga aatgaccgac 2400
caagcgacgc ccaacctgcc atcacgagat ttcgattcca ccgccgcctt ctatgaaagg 2460
ttgggcttcg gaatcgtttt ccgggacgcc ggctggatga tcctccagcg cggggatctc 2520
atgctggagt tcttcgccca ccccaacttg tttattgcag cttataatgg ttacaaataa 2580
agcaatagca tcacaaattt cacaaataaa gcatttttttt cactgcattc tagttgtggt 2640
ttgtccaaac tcatcaatgt atcttatcat gtctgtatac cgtcgacctc tagctagagc 2700
ttggcgtaat catggtcata gctgtttcct gtgtgaaatt gttatccgct cacaattcca 2760
cacaacatac gagccggaag cataaagtgt aaagcctggg gtgcctaatg agtgagctaa 2820
ctcacattaa ttgcgttgcg ctcactgccc gctttccagt cgggaaacct gtcgtgccag 2880
ctgcattaat gaatcggcca acgcgcgggg agaggcggtt tgcgtattgg gcgctcttcc 2940
gcttcctcgc tcactgactc gctgcgctcg gtcgttcggc tgcggcgagc ggtatcagct 3000
cactcaaagg cggtaatacg gttatccaca gaatcagggg ataacgcagg aaagaacatg 3060
tgagcaaaag gccagcaaaa ggccaggaac cgtaaaaagg ccgcgttgct ggcgtttttc 3120
cataggctcc gccccctga cgagcatcac aaaaatcgac gctcaagtca gaggtggcga 3180
aacccgacag gactataaag ataccaggcg tttccccctg gaagctccct cgtgcgctct 3240
cctgttccga ccctgccgct taccggatac ctgtccgcct ttctcccttc gggaagcgtg 3300
gcgctttctc atagctcacg ctgtaggtat ctcagttcgg tgtaggtcgt tcgctccaag 3360
ctgggctgtg tgcacgaacc ccccgttcag cccgaccgct gcgccttatc cggtaactat 3420
cgtcttgagt ccaacccggt aagacacgac ttatcgccac tggcagcagc cactggtaac 3480
aggattagca gagcgaggta tgtaggcggt gctacagagt tcttgaagtg gtggcctaac 3540
tacggctaca ctagaagaac agtatttggt atctgcgctc tgctgaagcc agttaccttc 3600

ggaaaaagag ttggtagctc ttgatccggc aaacaaacca ccgctggtag cggtttttt 3660
gtttgcaagc agcagattac gcgcagaaaa aaaggatctc aagaagatcc tttgatcttt 3720
tctacggggt ctgacgctca gtggaacgaa aactcacgtt aagggatttt ggtcatgaga 3780
ttatcaaaaa ggatcttcac ctagatcctt ttaaattaaa aatgaagttt taaatcaatc 3840
taaagtatat atgagtaaac ttggtctgac agttaccaat gcttaatcag tgaggcacct 3900
atctcagcga tctgtctatt tcgttcatcc atagttgcct gactcccccgt cgtgtagata 3960
actacgatac gggagggctt accatctggc cccagtgctg caatgatacc gcgagaccca 4020
cgctcaccgg ctccagattt atcagcaata aaccagccag ccggaagggc cgagcgcaga 4080
agtggtcctg caactttatc cgcctccatc cagtctatta attgttgccg ggaagctaga 4140
gtaagtagtt cgccagttaa tagtttgcgc aacgttgttg ccattgctac aggcatcgtg 4200
gtgtcacgct cgtcgtttgg tatggcttca ttcagctccg gttcccaacg atcaaggcga 4260
gttacatgat cccccatgtt gtgcaaaaaa gcggttagct ccttcggtcc tccgatcgtt 4320
gtcagaagta agttggccgc agtgttatca ctcatggtta tggcagcact gcataattct 4380
cttactgtca tgccatccgt aagatgcttt tctgtgactg gtgagtactc aaccaagtca 4440
ttctgagaat agtgtatgcg gcgaccgagt tgctcttgcc cggcgtcaat acgggataat 4500
accgcgccac atagcagaac tttaaaagtg ctcatcattg gaaaacgttc ttcggggcga 4560
aaactctcaa ggatcttacc gctgttgaga tccagttcga tgtaacccac tcgtgcaccc 4620
aactgatctt cagcatcttt tactttcacc agcgtttctg ggtgagcaaa aacaggaagg 4680
caaaatgccg caaaaaaggg aataagggcg acacggaaat gttgaatact catactcttc 4740
ctttttcaat attattgaag catttatcag ggttattgtc tcatgagcgg atacatattt 4800
gaatgtattt agaaaaataa acaaataggg gttccgcgca catttccccg aaaagtgcca 4860
cctgacgtc 4869

<210> 68
<211> 20
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence

<400> 68
ggggatcagc gtttgagtaa 20

<210> 69
<211> 20
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence

<400> 69
taggccccac ctccttctat 20

<210> 70
<211> 30
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence

<400> 70
tgcggatcca gagcagattg tactgagagt 30

<210> 71
<211> 29
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence

<400> 71
ctctatctcg agtgaggcgg aaagaacca 29

<210> 72
<211> 40
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence

<400> 72
tttaagcttg aagactattt ttacatcagg ttgtttttct 40

<210> 73
<211> 37
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized primer sequence

<400> 73
tttaagcttg aagacacggt gtttcgtcct ttccaca 37

<210> 74
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 74
caccgaagca gcacgacttc ttcttcaaga gagaagaagt cgtgctgctt c 51

<210> 75
<211> 51
<212> DNA
<213> Artificial

<220>
<223> An artificially synthesized sequence for siRNA

<400> 75
aaaagaagca gcacgacttc ttctcttctg aagaagaagt cgtgctgctt c 51